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<p>(21) International Application Number: PCT/US97/09955 (22) International Filing Date: 6 June 1997 (06.06.97) (30) Priority Data: 08/665,653 18 June 1996 (18.06.96) US (71) Applicant: ORTHO PHARMACEUTICAL CORPORATION [US/US]; U.S. Route 22 #202, Raritan, NJ 08869-0602 (US). (72) Inventors: KANOJIA, Ramesh, M.; 18 Jeffrey Court, Somerville, NJ 08876 (US). DEMERS, James, P.; Apart- ment 6N, 380 Riverside Drive, New York, NY 10025-1821 (US). HLASTA, Dennis, J.; 5008 Davis Drive, Doylestown, PA 18901 (US). JOHNSON, Sigmond, G.; 222 Nauthatch Court, Three Bridges, NJ 08887 (US). KLAUBERT, Dieter, H.; 29855 Fox Hollow Road, Eugene, OR 97405 (US). (74) Agents: CIAMPORCERO, Audley et al.; Johnson and Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933- 7003 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.</p>	
<p>(54) Title: DIARYL ANTIMICROBIAL AGENTS</p> <div style="text-align: center; margin: 20px 0;"> $\begin{array}{c} \text{G} \\ \diagup \\ \text{L} \text{---} (\text{J})_q \text{---} (\text{CH}_2)_m \text{---} \text{X} \text{---} \text{Ar} \text{---} (\text{W})_p \text{---} (\text{CH}_2)_n \text{---} \text{A} \\ \diagdown \\ \text{E} \end{array} \quad (1)$ </div> <p>(57) Abstract</p> <p>The invention relates to diaryl antimicrobial compounds of general formula (1), where G, E, L, J, q, m, X, Ar, W, p, n and A are as described herein, pharmaceutical compositions containing the compounds, methods for their production and their use in treating bacterial infections.</p>		

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DIARYL ANTIMICROBIAL AGENTS

Field of the Invention

The present invention relates to a novel method of treating bacterial
5 infections in mammals by administering a therapeutically effective amount of
a compound effective in inhibiting the action of a bacterial histidine protein
kinase. In another aspect, the invention relates to diaryl antibacterial
compounds, pharmaceutical compositions containing the compounds, and
10 methods for their production and use. These compounds are useful as anti-
infective agents against a variety of bacterial organisms, including organisms
which are resistant to other known antibiotics.

Background of the Invention

It is well established that prokaryotes regulate the transcription of
15 many of their genes in response to changes in the organisms' environment
(J. B. Stock, A. M. Stock, and J. M. Mottonen, *Nature*, **344**, 395-400 (1990)).
Such regulation is essential if the organism is to adapt itself to survival in a
changing environment, and pathogenic bacteria rely on such regulatory
systems to enable them to survive within their host's body (J. F. Miller, J. J.
20 Mekalanos, S. Falkow, *Science*, **243**, 1059 (1989)). Chemical compounds
that interfere with the regulatory mechanisms would be expected to be useful
anti-infective drugs, as they would prevent bacteria from making necessary
adaptive changes in their patterns of gene expression.

Virulence, chemotaxis, toxin production, sporulation, and reproduction
25 are examples of the bacterial processes that are under regulatory control,
and which could be inhibited by such compounds. The inhibition of one or
more of these processes is expected to lead to reduced virulence, a slowing
or halting of bacterial growth and reproduction, and even to bacterial cell
death if vital functions are interrupted.

30 For example, it has been shown that *Salmonella* species express
certain proteins, under regulatory control and in response to the presence of
epithelial cells, which enable them to adhere to and invade intestinal
epithelial cells. Bacteria lacking functional genes for these proteins are
avirulent: they cannot cause infection in mice (B. B. Finlay, F. Heffron, S.
35 Falkow, *Science*, **243**, 940-943 (1989)). A similar effect would be expected if
the genes coding for these proteins were intact, but remained unexpressed.

To accomplish adaptive responses to the environment, bacteria rely on
phosphorelay mechanisms, referred to in the art as a "two-component

switches." These switches have the net effect of transmitting information from the environment to the cell nucleus, where the information is responded to by the switching on or off of transcription of relevant genes. The first step of this phosphorelay scheme relies on numerous histidine protein kinase (HPK) enzymes. Most of these HPK enzymes are sensor molecules, and respond to stimulation by specific environmental signals by transferring phosphate from ATP to a histidine residue of the HPK protein. Some HPK enzymes are stimulated by the presence of acceptor proteins (described below), the concentration of which are modulated by environmental signals. In either case, this auto-phosphorylation is followed by transfer of the phosphate to an aspartyl residue of one or more acceptor proteins (the second components of the two-component switch), which are either regulators of gene expression (by binding to control regions on DNA, or to the RNA polymerase complex) or are themselves kinases for other acceptor molecules. These secondary acceptors may again be regulatory proteins, or kinases toward yet another protein. This cascade of phosphate from protein to protein eventually results in the phosphorylation of one or more regulatory proteins, which then control gene expression.

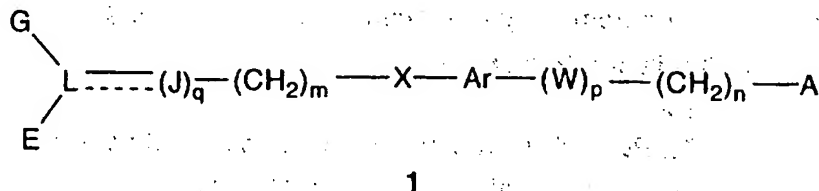
Mammalian cells do not, or at least are not presently known to, utilize HPK-driven phosphorelay systems for gene regulation. Thus, compounds which selectively inhibit either the autophosphorylation of the HPK protein, or the phosphotransfer step(s), or both, would not be expected to have undesirable effects on the host organism, and are promising candidates for anti-infective drugs. The emergence of drug-resistant pathogenic organisms that are resistant to one or more of the currently available drugs has created a need for novel antibiotics, that act by mechanisms unrelated to those of currently available agents, and inhibitors of HPK would fill this need. The presence of multiple HPK-driven systems in bacteria gives HPK inhibitors a potential advantage over current antibiotics, in that mutations of a single HPK enzyme are unlikely to confer drug resistance to an organism.

Recently, workers in this field reported a method for detecting bacterial "virulence" genes that are selectively expressed when bacteria infect a host (M. J. Mahan, J. M. Schlauch, and J. J. Mekalanos, *Science*, **259**, 686-688 (1993)). The potential use of this information in the design of new antibiotics was mentioned, but actual methods of reducing expression of these genes were not described. A preliminary report from another group of workers disclosed inhibitors of the two-component switch controlling alginate gene activation in *Pseudomonas aeruginosa* in an *in vitro* system (S.

Roychoudhury *et al.*; *Proc. Nat. Acad. Sci.*, **90**, 965-969 (1993)), but no anti-bacterial activity of the compounds was reported.

Summary of the Invention

5 The invention comprises compounds of the general Formula 1 shown below:

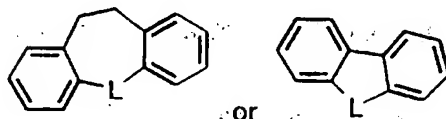


10 wherein

L is selected from the group consisting of N, CH and C;

G and E are independently selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), phenylC₁₋₄alkyl, substituted phenylC₁₋₄alkyl (where the phenyl substituents are hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl and 3-thienyl, or may be taken together with L, (when L is CH), to form

20



or

J is CH or O;

q is 0 or 1;

m is 0-6;

25 X is selected from the group consisting of O, S, NR and -C(O)NR- where R is hydrogen, C₁₋₆alkyl and phenylC₁₋₄alkyl;

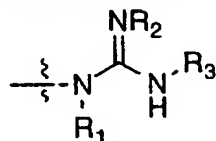
Ar is aryl or substituted aryl (where the aryl substituents are hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), wherein aryl is phenyl, biphenyl or naphthyl;

30 p is 0 or 1

W is O or S

n is 0-6

A is selected from the group consisting of NR_1R_2 , $N+R_1R_2R_3 \cdot Z^-$.



, amidino, CO_2H , $CH(R_4)CO_2H$, $CH=CHR_5$, $CH=C(CO_2H)_2$, halogen, phthalimido and a heterocycle, optionally substituted with 1-3 substituents (where the substituents are selected from C_{1-6} alkyl, phenyl C_{1-4} alkyl, formyl, C_{1-3} alkylcarbonyl and trifluoroalkylcarbonyl),

wherein:

R_1 , R_2 , and R_3 are independently selected from hydrogen, C_{1-6} alkyl, and phenyl C_{1-6} alkyl;

R_4 is hydrogen or hydroxy;

R_5 is CO_2H or $C(O)NH(CH_2)_tOH$ where t is 1-4;

Z^- is a pharmaceutically acceptable counterion;

heterocycle is a saturated or unsaturated, charged or uncharged 5 to 6 membered monocyclic ring which has 1, 2, or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur atoms;

with the proviso that:

when q is 1 and J is CH , L is C , m is at least 1 and the dashed line is taken together with the solid line to form a double bond;

when q is 1 and J is O , L is CH , m is at least 2 and the dashed line is absent;

when q is 0, L is N or CH and the dashed line is absent;

when q and m are 0, L is CH ;

when n is 0, A may also be hydroxy;

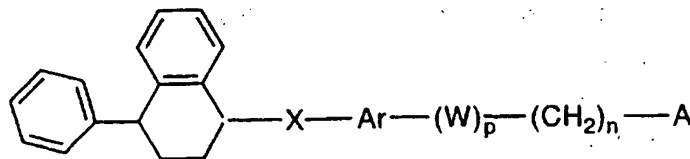
when X is $C(O)NH$, A is not CO_2H ; and

where n is 0 or 1, and W is O or S , A is not OH , NR_1R_2 or a heteroatom;

and the pharmaceutically acceptable salts and prodrug forms thereof.

An additional aspect of the invention comprises compounds of the

Formula II



II

4

wherein:

X is selected from the group consisting of O, S, NR and -C(O)NR-
where R is hydrogen, C₁₋₆alkyl and phenylC₁₋₄alkyl;

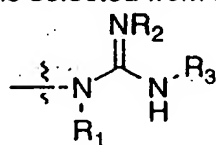
Ar is aryl or substituted aryl (where the aryl substituents are
hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), wherein
aryl is phenyl, biphenyl or naphthyl;

p is 0 or 1

W is O or S

n is 0-3

A is selected from the the group consisting of NR₁R₂, N⁺R₁R₂R₃ • Z⁻,



, amidino, CO₂H, CH(R₄)CO₂H, CH=CHR₅,
CH=C(CO₂H)₂, halogen, phthalimido and a heterocycle, optionally
substituted with 1-3 substituents (where the substituents are
selected from C₁₋₆alkyl, phenylC₁₋₄alkyl, formyl, C₁₋₃alkylcarbonyl
and trifluoroalkylcarbonyl),

wherein:

R₁, R₂, and R₃ are independently selected from
hydrogen, C₁₋₆alkyl, and phenylC₁₋₆ alkyl;

R₄ is hydrogen or hydroxy;

R₅ is CO₂H or C(O)NH(CH₂)_tOH where t is 1-4;

Z⁻ is a pharmaceutically acceptable counterion;

heterocycle is a saturated or unsaturated, charged or
uncharged 5 to 6 membered monocyclic ring which has 1, 2, or
3 heteroatoms independently selected from oxygen, nitrogen
and sulfur atoms;

with the proviso that:

when n is 0, A may also be hydroxy;

when X is C(O)NH, A is not CO₂H; and

where n is 0 or 1, and W is O or S, A is not OH, NR₁R₂ or a
heteroatom;

and the pharmaceutically acceptable salts and prodrug forms thereof.

The compounds of the present invention inhibit the
autophosphorylation of bacterial histidine kinases; they also inhibit th
transfer of phosphate from phosphorylated histidine kinases to the phosphate

acceptor proteins involved in regulation of bacterial gene expression. The compounds of the present invention have been found to inhibit the growth of bacteria by the standard method, measurement of minimum inhibitory concentrations (MIC values). The compounds are useful as bacteriostatic and bactericidal agents, and as anti-infective agents in the treatment of infectious diseases. Thus, one aspect of the invention comprises a method of treating bacterial infections in mammals by administering to a mammal suffering from such infection a therapeutically effective amount of a compound selected from those of Formula 1.

Preferred embodiments of the invention are the compounds where X is O or S, Ar is phenylene, and where A carries a charge at physiological pH. More preferred are the embodiments where A is amino, guanidino, or comprises a quaternary nitrogen.

15 Detailed description of the invention.

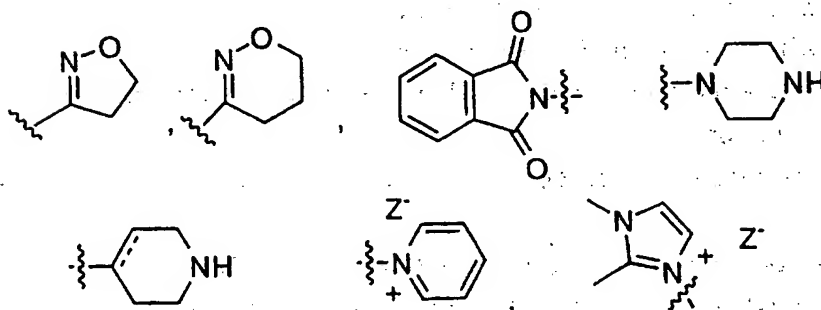
Relative to the above generic description, certain compounds of Formula I are preferred.

Preferred groups for G and E are phenyl and substituted phenyl.

20 Preferred groups for X are O and S.

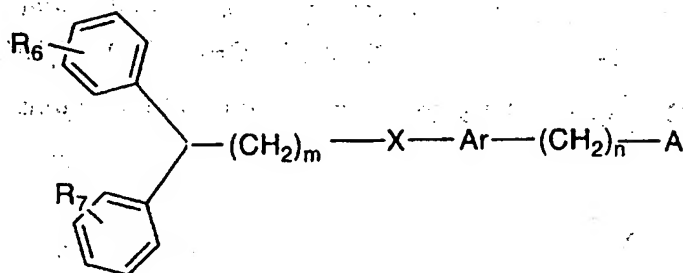
Preferred groups for Ar are 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,6-naphthylene, 6,1-naphthylene, 1,5-naphthylene, 2,5-naphthylene, 5,2-naphthylene, or 2,6-naphthylene.

25 Preferred groups for A are NR_1R_2 , guanidino, CO_2H , halogen, $\text{CH}=\text{CHCO}_2\text{H}$, $\text{CH}=\text{CHC}(\text{O})\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{CH}(\text{OH})\text{CO}_2\text{H}$, $\text{CH}=\text{C}(\text{CO}_2\text{H})_2$, $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ Z^- , and moieties of the formulae:



30 particularly those which carry a charge at physiological pH.

Most preferred of the compounds of Formula I are those of Formula III:



III

wherein

R₆ and R₇ are independently selected from H, halogen, C₁-6alkyl and C₁-6alkoxy;

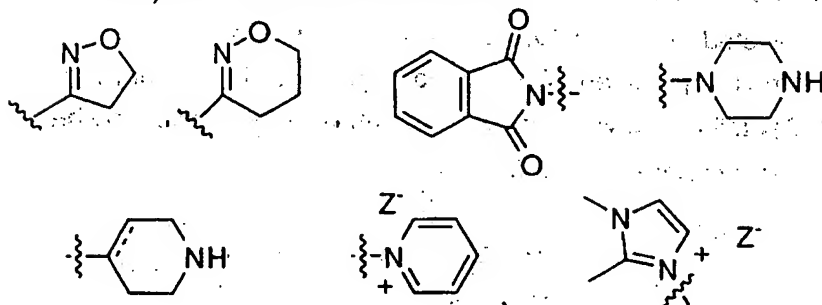
m is 1 or 2;

X is selected from O, and S;

Ar is selected from 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; wherein Ar may optionally be further substituted with one to three substituents selected from halogen, C₁-6alkyl, hydroxy, or C₁-6alkoxy;

n is 1, 2, or 3;

A is selected from NR₁R₂, guanidino, N⁺R₁R₂R₃ Z⁻ (wherein R₁, R₂, and R₃ are independently H, C₁-6alkyl, or aryl-C₁-6alkyl and wherein Z⁻ is a pharmaceutically acceptable anion) and moieties of the formula:



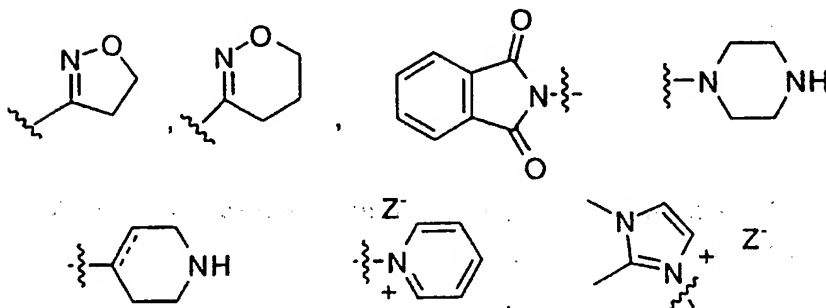
With respect to compounds of Formula II, the preferred groups are as follows:

Preferred groups for X are O and S.

Preferred groups for Ar are 1,2-phenylene, 1,3-phenylene,

1,4-phenylene, 1,6-naphthylene, 6,1-naphthylene, 1,5-naphthylene,
2,5-naphthylene, 5,2-naphthylene, or 2,6-naphthylene;

Preferred groups for A are NR_1R_2 , guanidino, CO_2H , 5-tetrazolyl,
halogen, $\text{CH}=\text{CHCO}_2\text{H}$, $\text{CH}=\text{CHC}(\text{O})\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{CH}(\text{OH})\text{CO}_2\text{H}$,
5 $\text{CH}=\text{C}(\text{CO}_2\text{H})_2$, $\text{N}^+\text{R}_1\text{R}_2\text{R}_3 \text{Z}^-$, and moieties of the formulae:



particularly those which carry a charge at physiological pH.

10

Most preferred of the compounds of Formula II are those in which:

X is selected from O, and S;

p is 0;

n is 0-3;

15

Ar is selected from 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene;

wherein Ar may optionally be further substituted with one to three
substituents selected from halogen, C₁-6alkyl, hydroxy, or C₁-6alkoxy; and

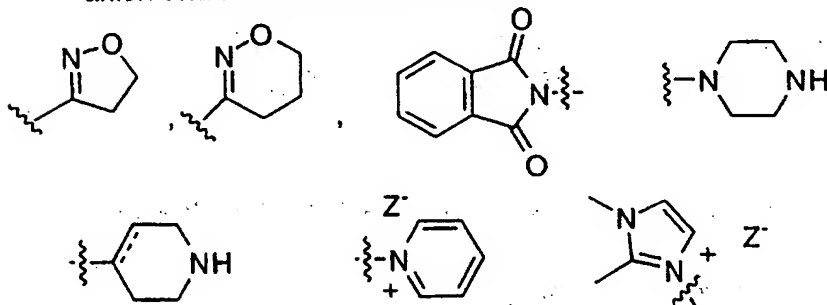
A is selected from NR_1R_2 , guanidino, $\text{N}^+\text{R}_1\text{R}_2\text{R}_3 \text{Z}^-$

wherein R, R₁, R₂, and R₃ are independently H, C₁-6alkyl, or

20

aryl-C₁-6alkyl and wherein Z⁻ is a pharmaceutically acceptable

anion and moieties of the formula:

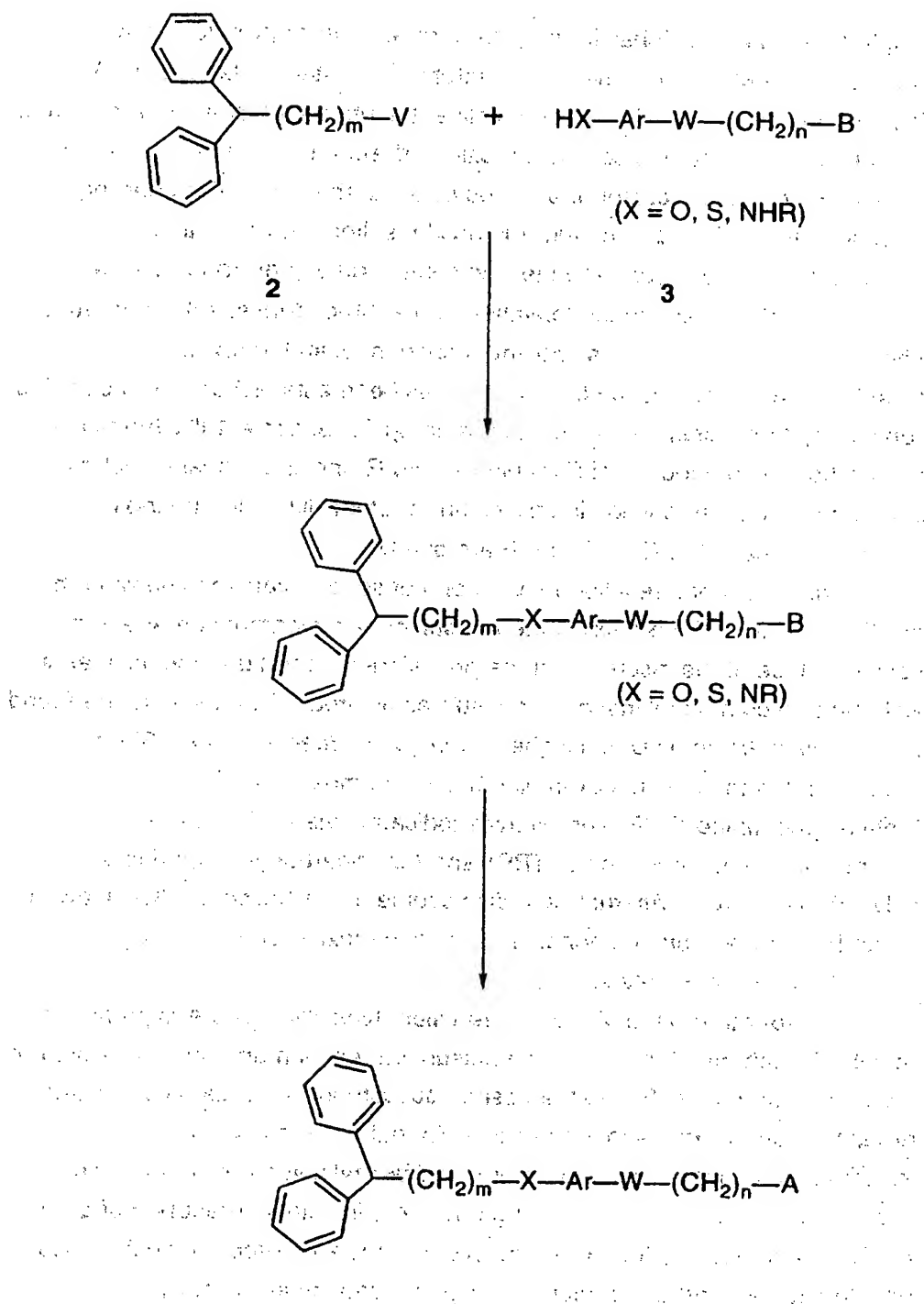


The compounds of Formula I, when L is CH and X is O, S, or NR, may
be prepared as shown in Scheme 1, by a Mitsunobu reaction (2, V=OH) or a

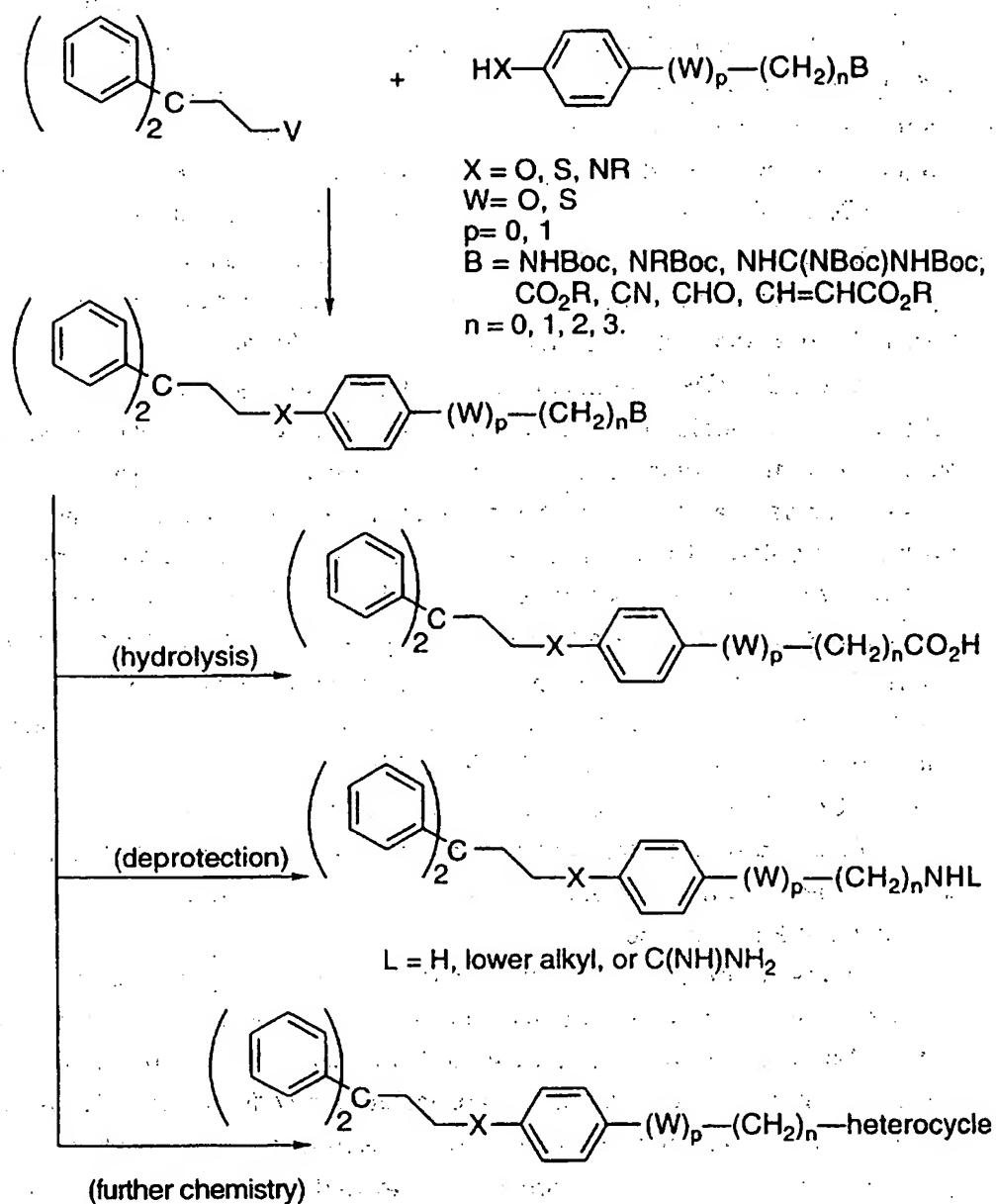
coupling reaction (2, V=halide, sulfonate, or another appropriate leaving group). In the Mitsunobu, the appropriately substituted arylalkanol (2, V = OH) and intermediate 3 (phenol derivative, thiophenol derivative, or naphthol derivative), are treated under the conditions described hereinafter, wherein B is the moiety A, its precursor or a protected A. In the alternative coupling reaction, intermediate 2, wherein V is halide, sulfonate, or another appropriate leaving group, and the aryl compound 3 (aniline derivative, phenol derivative, thiophenol derivative, or naphthol derivative) are treated with a suitable base, such as sodium hydride, sodium hydroxide, or potassium carbonate. Once the linker X has been established, the group B is converted, if necessary, into the desired group A. Scheme 1 illustrates the preparation of compounds of Formula I where G and E are phenyl, but it is understood that the reaction is applicable for other diaryl compounds, particularly when G or E, or G and E are pyridyl.

The Mitsunobu reaction may be one of several variants known in the art; the selection of the appropriate phosphine, azodicarbonyl reagent, and solvent will be at the discretion of the practitioner, based on empirical results with the particular combination of substrates desired. Guidance can be found in the review article by D. L. Hughes, in *Organic Reactions*, **42**, 335-656 (1992), and in the detailed examples below. In most cases triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD), or alternatively tributylphosphine (TBP) and (azodicarbonyl)dipiperidine (ADDP), will suffice. Alternatively, displacement of a halide or other leaving group by the appropriate phenoxide or thiophenoxide can be used to generate the O or S linkers.

In order to run the Mitsunobu reaction, typically group A is protected as moiety B. Scheme 2 illustrates the Mitsunobu reaction and the conversion of the precursor, moiety B, into the desired substituent A. Suitable protecting groups for guanidines and amines include, but are not limited to, trifluoroacetyl, t-butoxycarbonyl (Boc), and benzyloxycarbonyl. In some cases B is not merely a protecting group but a functional precursor of group A. This is particularly true when the desired A is a heterocycle such as 4,5-dihydrooxazole and the precursor is hydroxyethylaminocarbonyl.



Scheme 1



Scheme 2

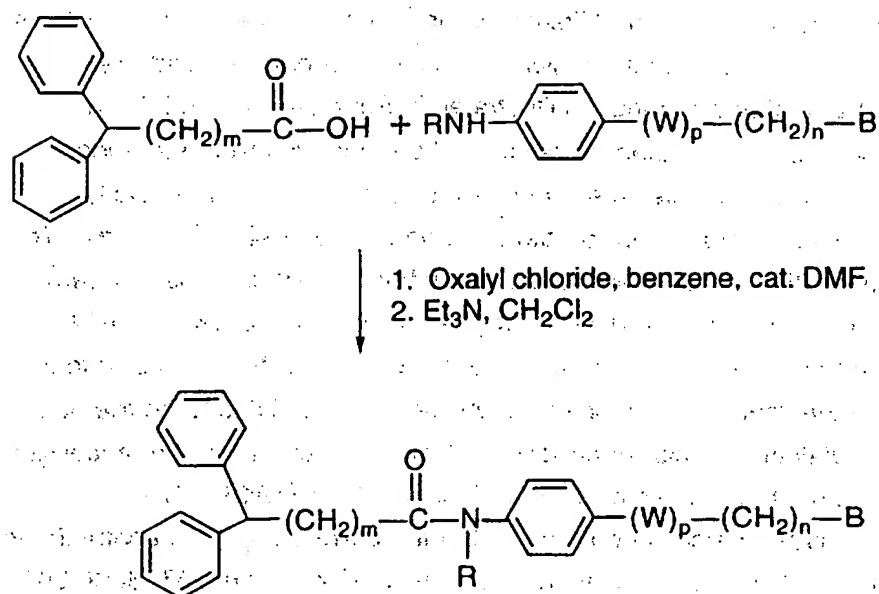
Suitable protecting groups for carboxylic acids include, but are not limited to, lower alkyl esters or benzyl esters; suitable precursor groups include olefin, nitrile, or oxazolidine. For cases where $\text{B} = \text{NHBoc}$, $\text{NHC}(\text{NBoc})\text{NHBoc}$, CO_2R , or $\text{CH}=\text{CHCO}_2\text{R}$, the intermediates are

deprotected after the Mitsunobu reaction to afford amines, guanidines or carboxylic acids, respectively. For cases where $B = \text{CN}$, the nitrile may be hydrolyzed to a carboxylic acid, reduced to provide an amine, or converted to a tetrazole; where $B = \text{an olefin}$, it may be oxidized with ozone or other reagents to provide an aldehyde or acid. Where $B = \text{CHO}$, NHBoc , CO_2R , or $\text{CH}=\text{CHCO}_2\text{R}$, the compounds may be converted into those of structure 1 where A is one of the heterocycles described. In the cases where A is a piperidine or piperazine, the terminal nitrogen is protected during the Mitsunobu reaction in the manner described above for amines.

Where $B = \text{CHO}$, reduction to the corresponding alcohol and subsequent conversion to the chloride (1, $A = \text{Cl}$) followed by reaction with a nitrogen-containing heterocycle, permits preparation of quaternary heterocyclic values of A, such as the pyridinium and imidazolium derivatives exemplified below. The chloride can also be used to quaternize tertiary aliphatic amines, giving 1 where $A = \text{N}^+\text{R}_1\text{R}_2\text{R}_3$, or may be reacted with primary or secondary amines to give cases where $A = \text{NR}_1\text{R}_2$. Compounds where $B = \text{CHO}$ are also useful precursors to acids *via* oxidation, to alcohols *via* reduction, to the phenol (if $n=0$ and p is 0) by Baeyer-Villiger oxidation, and to alpha-hydroxy acids ($A = \text{CH}(\text{OH})\text{COOH}$) *via* addition of trihalomethyl anions. Specific examples of these processes are to be found below.

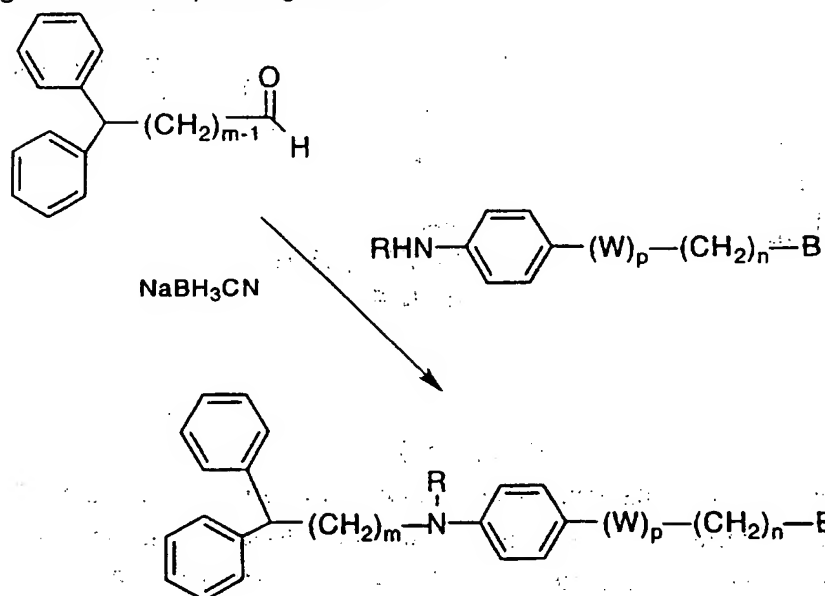
To prepare those olefin compounds of Formula I which have a double bond on the L group, a diaryl allylic alcohol can be substituted for intermediate 2 in Scheme 1.

In cases where $X = \text{C}(\text{O})\text{NR}$ a coupling reaction to generate the linker X is performed with the appropriately substituted acid and the appropriately substituted aniline derivative as illustrated in Scheme 3. In Scheme 3, Ar is 1,4-phenylene, but the methods are applicable to any definition of Ar. As with the Mitsunobu reaction, it will sometimes be necessary that group B is a precursor or protected form of group A, as defined as in Scheme 2, and is subsequently converted into the desired group A as in Scheme 2. In general, the carboxylic acid partner of the coupling reaction is activated with one of a variety of reagents, such as carbonyldiimidazole (CDI), thionyl chloride, oxalyl chloride, or a carbodiimide reagent such as dicyclohexylcarbodiimide (DCC). The coupling reactions may be chosen from, but are not limited to, those illustrated in the scheme and described further below. There are a wide variety of coupling methods known to one skilled in the art, and the majority of them would be applicable to the reaction in Scheme 3.



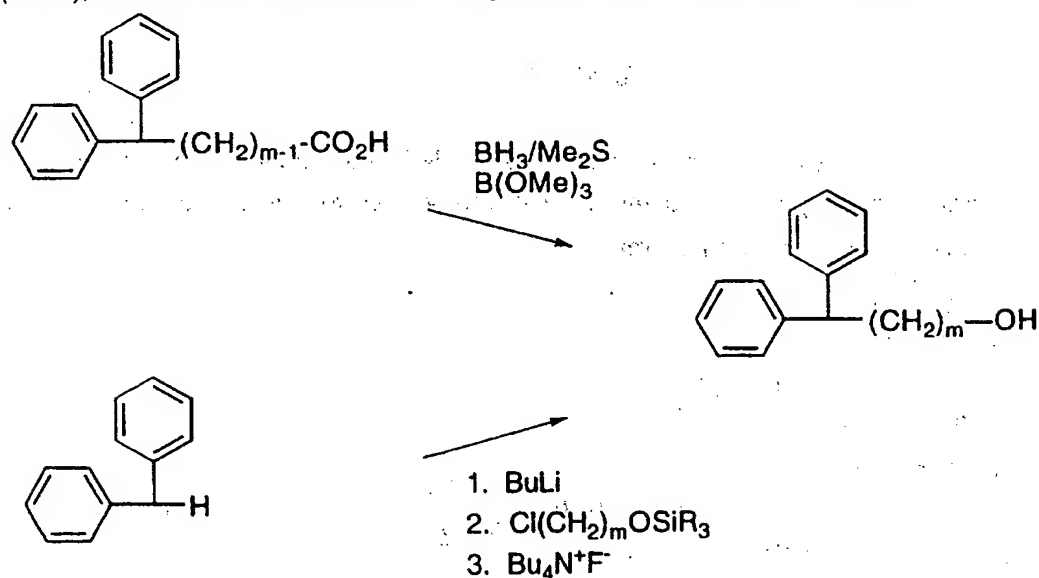
Scheme 3

To prepare compounds where X = NR, Scheme 4 may be used. A known aldehyde is reductively aminated with an aniline using NaBH₄CN to give the corresponding amine.



Scheme 4

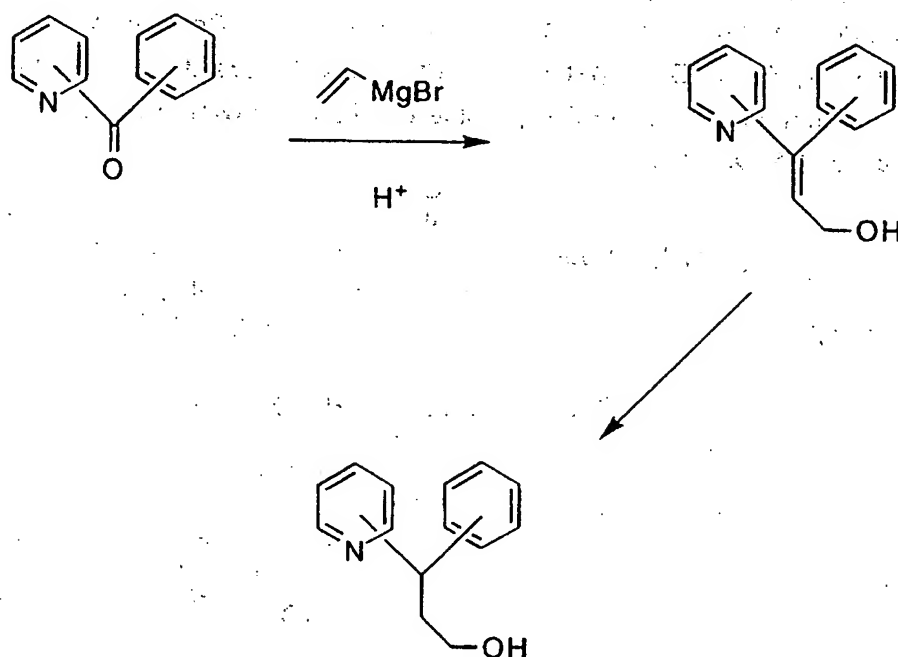
The starting materials for the Mitsunobu, acylation, coupling and reductions of Schemes 1-3 are, in general, known classes of compounds, and are prepared by routine methods, as illustrated in Schemes 5,6 and 7. In Scheme 5, many of the diarylalkanoic acid and diarylmethane starting materials, as well as substituted derivatives thereof, are commercially available. The others can be prepared by various published methods. The conversion of the acids to diarylalkanols by borane reduction is a known synthesis (M. Said *et al.*, *Biochem. Biophys. Res. Comm.*, **187**, 140-145 (1992)), modified in the present case by the addition of trimethyl borate to accelerate the reaction. The chain-extension of a diarylalkanol to the next higher diarylalkanoic acid then makes the next higher value of *m* accessible (McPhee, Lindstrom, *J. Amer. Chem. Soc.*, **65**, 2177 (1943). The diarylalkanols may also be prepared from the corresponding diarylmethanes as shown (C. G. Screttas, M. Micha-Screttas, *J. Org. Chem.*, **47**, 3008-3011 (1982), also H. W. Gibson *et al.*, *J. Org. Chem.*, **58**, 3748-3756 (1993)).



Scheme 5

To prepare the Mitsunobu starting material where G or B is pyridyl, a combination of literature procedures is used as illustrated by Scheme 6. Hogberg *et al.*, *J. Org. Chem.* **1984**, **22**, 4209-4214, Wolffenstein R. *et al.* *Chem Ber.* **1915**, **48** 2043. The starting ketone is prepared from the appropriate pyridyl acyl chloride and benzene, by the method of Wolffenstein. This ketone is treated with vinyl magnesium bromide and rearranged with

- aqueous acid to give the depicted allylic alcohol as described by Hogberg. This alcohol is treated with H_2 at elevated pressure to give the saturated alcohol. This procedure can be adapted to give any pyridyl substitution by using commercially available intermediates. If one desires compounds
- 5 where G and B are both pyridyl, those compounds can be prepared by acylating lithiated pyridines with pyridyl acyl halide according to literature procedures. Cochenne, C., *et al.* *Synthesis* 1995, 3, 321-324.



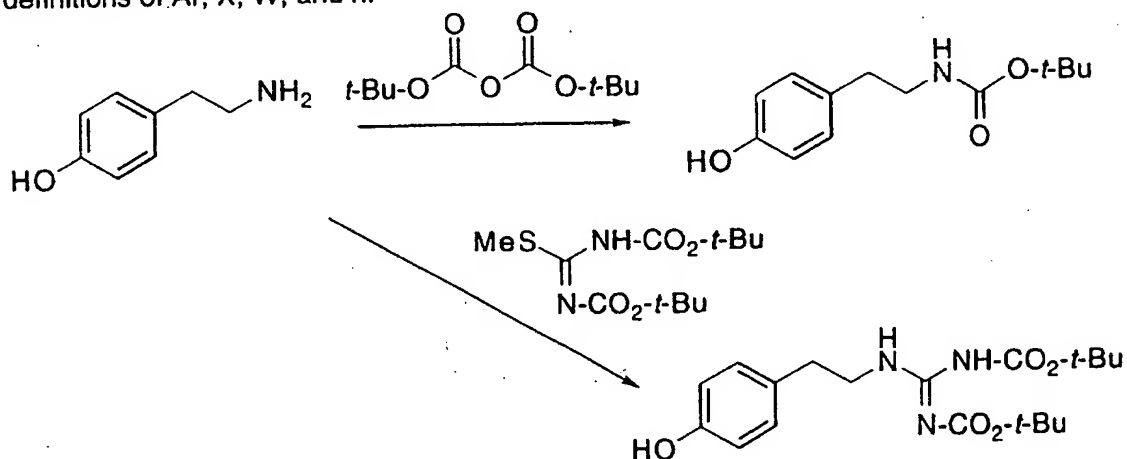
Scheme 6

10

- In Scheme 7, reaction of 2-(4-hydroxyphenyl)ethylamine with di-*t*-butyldicarbonate, to afford a protected phenolic coupling component for the Mitsunobu reaction, is illustrated. A variety of (hydroxyphenyl)alkylamines and (hydroxyphenoxy)alkylamines are commercially available or are known
- 15 compounds; they can be synthesized by common methods such as reductive amination of benzaldehydes, hydrogenation of arylacetonitriles or aryloxyacetonitriles, reduction of cinnamides or cinnamylamines, etc. Methods for their preparation can be chosen from, but are not limited to, the examples presented herein. Where X is S, 4-mercaptobenzaldehyde may be

coupled *via* the Mitsunobu reaction to the desired diarylalkanol, and the aldehyde then converted to the desired group $(CH_2)_n-A$ or $(CH_2)_n-B$ by the methods discussed below.

- Also in Scheme 7, the generation of a protected guanidine from the corresponding amine is illustrated, again providing a phenolic component for the Mitsunobu coupling. The illustrated use of *N,N'*-bis(*t*-butoxycarbonyl)-*S*-methylisothiurea for this purpose is a known procedure (R. J. Bergeron, J. S. McManis, *J. Org. Chem.*, **52**, 1700-1703 (1987), it is in some cases improved by the addition of silver acetate to the reaction mixture. (See also M. S. Bernatowicz, Y. Wu, G. R. Matsueda, *Tetrahedron Letters*, **34**, 3389 (1993)). These methods are in general applicable to all amines with the various definitions of Ar, X, W, and n.



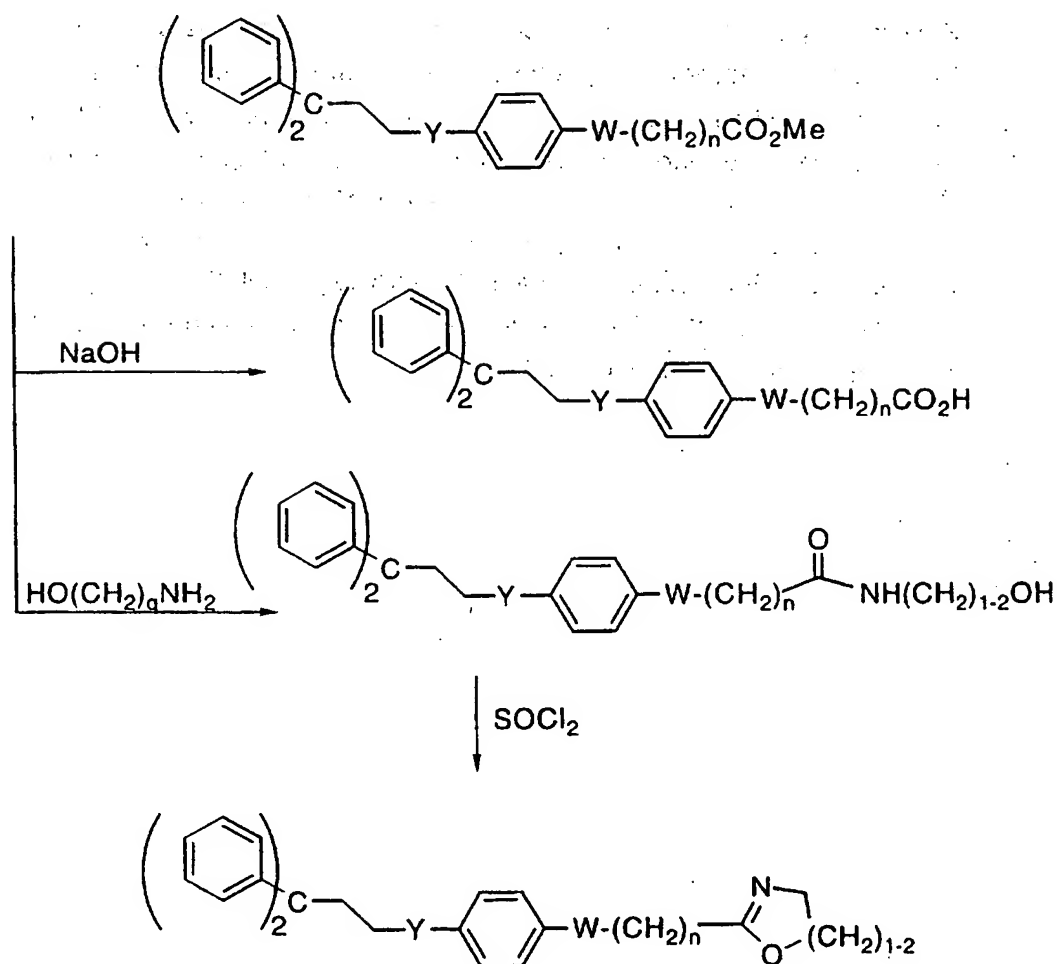
Scheme 7

- Alternatively, one can prepare 1 with $A = \text{NH}_2$ and then convert the amino group into a guanidino group by the above or by other known methods (e.g., M. S. Bernatowicz, Y. Wu, G. R. Matsueda, *J. Org. Chem.*, **57**, 2497-2502 (1992) and references therein).

- Scheme 8 illustrates the preparation of compounds where $A = \text{CO}_2\text{H}$, and conversion of these to *N*-(hydroxyalkyl)amides, followed by cyclization to give the claimed 3,4-dihydro-1,2-oxazine derivatives. The starting omega-(hydroxyphenyl)alkanoic esters (or the corresponding acids) in Scheme 8 are known compounds; novel examples with further substitution on the ring can be prepared as described further below, or by other methods known to the art. For example, beginning with optionally substituted 4-hydroxy or 4-methoxy benzaldehydes, one can obtain the case where $n = 0$ by oxidation (B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.*, **27**, 888 (1973)), where $n = 1$

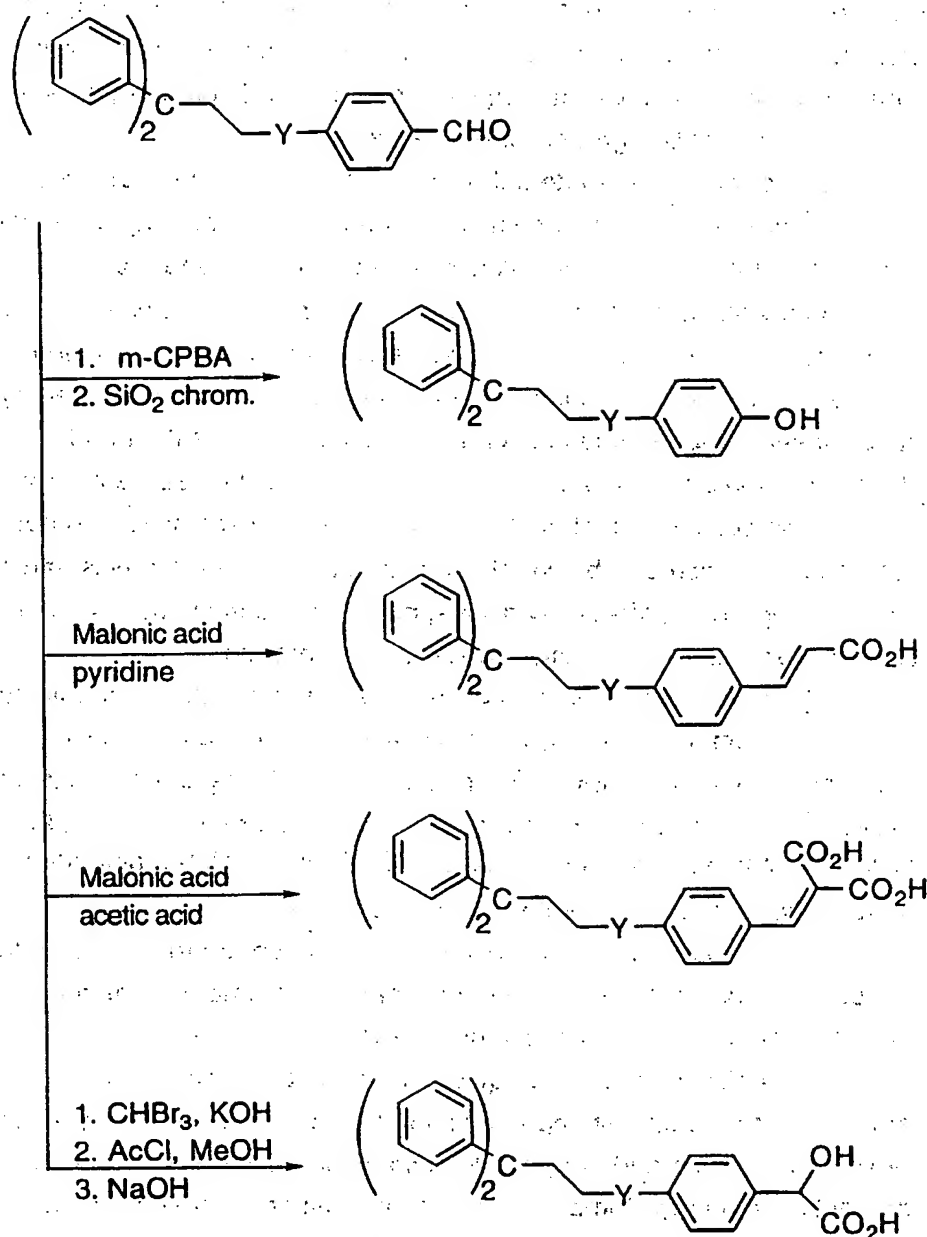
- by chain extension (K. Shaw, M. Armstrong, A. McMillan, *J. Org. Chem.*, **21**, 1149 (1956)), where $n = 2$ by condensation with malonic acid to give the cinnamic acid (J. Koo et al., *Org. Syn. coll. vol. IV*, 327 (1963)), followed by hydrogenation if desired, and where $n = 3$ by homologation with a phosphorous ylide (J. G. Cannon et al., *J. Med. Chem.*, **32**, 2210 (1989)), again followed by hydrogenation if desired. As shown in Scheme 9, these reactions can also be performed on **1** where $A = \text{CHO}$, giving the corresponding acids directly; these methods are also applicable to the other disclosed definitions of Ar.

10



Scheme 8

- When n is 0 and A is CHO , as illustrated in Scheme 9, one may perform a Baeyer-Villiger oxidation on **1** to obtain the phenol wherein n is 0 and A is OH , and then O-alkylate this phenol via appropriate Mitsunobu or nucleophilic displacement reactions as described above to attach the group $(\text{CH}_2)_nA$ or $(\text{CH}_2)_nB$, thereby obtaining the cases where W is oxygen. Alternatively, one can submit the known compounds 2-(phenylsulfonyloxy)phenol or 3-(phenylsulfonyloxy)phenol to the reactions of Scheme 1, and then remove the phenylsulfonyl group by hydrolysis. Examples of both approaches to the cases where W is oxygen are provided below.
- Where it is desired that W be sulfur, a suitable precursor group is nitro. For example, one would submit 4-nitrophenol to the Mitsunobu reaction of Scheme 1, generating an intermediate where $n = 0$ and B is a nitro group. Reduction, diazotization and reaction with a xanthate (the Leuckart thiophenol synthesis, see D. S. Tarbel, *J. Amer. Chem. Soc.*, **74**, 48 (1952)), provides the thiophenol, and alkylation with an alkylating agent such as $\text{Br}(\text{CH}_2)_nA$ or $\text{Br}(\text{CH}_2)_nB$ then provides access to the desired material.
- In addition, as illustrated, Scheme 9, may be used to prepare compounds of Formula I, where A is $\text{CH}=\text{CHCO}_2\text{H}$, $\text{CH}=\text{C}(\text{CO}_2\text{H})_2$, $\text{CH}(\text{OH})\text{CO}_2\text{H}$ and the like. The starting material are the compounds of Formula I where n is 0 and A is CHO .

**Scheme 9**

The foregoing reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformations proposed. This will frequently necessitate

judgment as to the order of synthetic steps, protection of reactive groups, and selection of reaction conditions. Reaction conditions compatible with the substituents employed will be apparent to one skilled in the art, as will be the selection of protecting groups where needed.

- 5 From formula I it is evident that some of the compounds of the invention may have one or more asymmetrical carbon atoms in their structure. It is intended that the present invention include within its scope the stereochemically pure isomeric forms of the compounds as well as their racemates. Stereochemically pure isomeric forms may be obtained by the application of known methods. Diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereospecific reactions.

- 20 Suitable pharmaceutical salts are those of inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, methanesulfonic acid, nitric acid, phosphoric acid, acetic acid, succinic acid, oxalic acid, malic acid and the like. Suitable salts are also those of inorganic or organic bases, such as KOH, NaOH, Ca(OH)₂, Al(OH)₃, piperidine, morpholine, ethylamine, triethylamine and the like.

- 25 Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

- 30 The ability of bacteria to quickly respond to changes in the environment is of utmost importance for their survival. Bacteria are capable of rapidly responding and adapting to such diverse stimuli as changes in nutrients, osmolarity, temperature, light, or host environment. These responses may be transient, such as those required for changes in motility or for entry into a host cell. Alternatively, the responses may require major shifts in gene expression and cell morphology, such as those required for sporulation, or for survival within a macrophage. The mechanism by which bacteria are able to sense cues from the physical environment (or from within the cytoplasm) and process these signals into appropriate responses often involves the so-called "two-component" systems.

35 As stated above, the treatment method of the present invention is based on the inhibition of this "two-component switch" system. All bacteria

us this mechanism to control various adaptive/virulence factors to facilitate establishment of a bacterial population in the environment (which is a bacterial infection in the host). The system invariably consists of a sensor which either activates a kinase or is a part of the kinase, and which upon stimulation, autophosphorylates. This phosphorylated species is a highly active phosphodonor which immediately transfers its phosphate to a "regulatory" component, which in turn initiates the biological response such as transcription or further phosphotransfer in a cascade which eventually ends in regulation of bacterial gene expression. Although each of the kinases and response regulators has a unique sequence (in fact, even functionally identical proteins have slightly different sequences in different species) they share a homologous biochemical mechanism and they share significant homology in the active site.

As stated, the present invention provides compounds which exhibit anti-microbial activity by inhibiting the autophosphorylation of bacterial histidine kinases. They also inhibit the transfer of phosphate from phosphorylated histidine kinases to the phosphate acceptor proteins involved in regulation of bacterial gene expression.

This invention further provides a method of treating bacterial infections in warm-blooded animals, which comprises administering to the animals a compound of the invention alone or in a mixture with a diluent or in the form of a medicament according to the invention.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing for example, from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and elixirs containing, for example, from about 20% to 50% ethanol, and the like; or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT, and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose.

Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to about 400 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in

sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

The compounds of the present invention have antibacterial activity as determined by the following tests. First, the compounds were tested for their activity in inhibiting the autophosphorylation of Kinase A and the transphosphorylation of Spo0F, two proteins involved in one of the above described signal transduction systems controlling gene expression in bacteria. Representative compounds were then tested for antibacterial activity against selected organisms by the standard MIC method. The results are set forth below.

Table 1 lists examples of compounds of the invention, along with their IC₅₀ values in the HPK *in vitro* assay described below, and MIC value ranges for the selected microorganisms identified below. These examples are merely illustrative of the invention, and are not intended to limit the scope of the claims in any way.

Table 1.

Cpd. #	IC ₅₀ μ M	MIC (G ⁺ /G ⁻)
2	31.25	
3	21.5	
4	19.8	6.2->50
6	68.9	
7	60	2-32
8	42.9	4->128
9	41	

	10	68	32->128
	11	19.5	8->128
	12	165	
	13	379.4	
5	14	130.4	
	15	45.6	
	17	643.5	
	18	>100	4->64
	20	>500	
10	21	>500	
	22	73	
	23	60	
	24	769	
15	25	313	

The protocols for the above referenced assays are as follows.

1. Autophosphorylation of Kinase A and Transphosphorylation of Spo0F

Assay

20 To study the effect of the compounds of the present invention on the signal transduction process in bacteria, the inhibiting effect of the compounds on the sporulation operon proteins Kinase A and Spo0F was examined. Specifically, the inhibition of autophosphorylation of Kinase A and the transphosphorylation of Spo0F was determined in the following assays. The
25 Spo0F response regulator is the primary substrate for phosphorylation by the protein kinase, Kin A, involved in the sporulation process in bacteria. See D. Burbulys, K.A. Trach, J.A. Hoch, *Cell*, 64, 545-552 (1991).

The following stock reagents were either prepared and used promptly or stored at the indicated temperature:

30 8 X Salts : 2 M KCl (5 mL), 1 M MgCl₂ (800 mL), 1 M CaCl₂ (100 mL), 10 mg/mL phenylmethylsulfonyl fluoride (200 mL), 1 M dithioreitol (50 mL), 0.25 M Na₂EDTA (32 mL) and H₂O 3.82 mL (-20 °C)

35 5X Loading Dye: 0.5M TRIS-HCl-pH 6.8 (7.5 mL), 10% SDS (2 mL) 0.1% bromophenol blue (0.5 mL), 100% glycerol (3 mL) and 12.5 M 2-mercaptoethanol (0.3 mL)

1-1.3 mg/mL KinA: 15 mM TRIS-HCl, pH 8.0, 6 mM KCl; 4 mM 2-mercaptoethanol; 40% glycerol (-20 °C)

1 mg/mL Spo0F: 17.5 mM TRIS-HCl, pH 8.0; 0.7 mM KCl; 0.7 mM
5 MgCl₂; 0.7 mM CaCl₂; 5 mM 2-mercaptoethanol; 30% Glycerol (-20 °C)

5% Stacking-Gel: 40% 29:1 acrylamide:bis acrylamide (1.25 mL),
0.5 M TRIS-HCl, pH 6.8 (2.5 mL), 10% SDS (0.1 mL), D-H₂O (6.15 mL)
10% ammonium persulfate (100 mL) and TEMED (25 mL)

10

SDS Running Buffer: TRIS-BASE (3.02 g), glycine (14.4 g),
SDS (1 g), D-H₂O (to 1 L)

The reaction mixture was prepared from 8X Salts (87 µL), 1M TRIS, pH
15 8 (118 µL), 50% glycerol (63 µL), Spo0F (14.1 µL) and KinA (7.0 µL).

Microcentrifuge tubes were charged with the reaction mixture (18.5 µL) and a
1.0 mM solution of the test compound in 5% DMSO (18.5 µL), and incubated
for 15 min on ice. 100 mM ATP solution (3.0 µL, containing 625 µCi [³²P]ATP)
was added, and the mixture left for 10 minutes at room temperature. The
20 reaction was quenched with 5X loading dye (10 µL per tube) and the
samples were loaded on a prepared 5% Stacking Gel, or stored on dry ice
until ready for use. The prepared wells were filled with SDS Running Buffer,
samples were loaded into the wells, and 80 volts were applied to the gel until
the dye front reached the bottom of the stacking gel. The voltage was then
25 increased to 250 volts until electrophoresis was complete. Radioactive
bands in the gel corresponding to phosphorylated KinA and Spo0F were
imaged and quantitated with a phosphorimager.

If either enzyme was inhibited (as evidenced by the absence of
labelled protein in the developed gel), an IC₅₀ was calculated by running the
30 assay with a range of inhibitor concentrations from 1 to 500 µM. After
electrophoresis of the reaction mixtures, percent inhibition was determined by
measuring the concentration of radioactive phosphorus with a
phosphorimager and calculating the values using a software program (BioRad
Molecular Analyst).

35

2. MIC Antimicrobial Assay

The *in vitro* antimicrobial activity of the compounds was determined by
the microdilution broth method following the test method from the National

Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A2, Vol.10, No.8 "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically - Second Edition."

5 In this method two-fold serial dilutions of drug in cation supplemented Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFUs/well).

10 Following inoculation of the microdilution trays, the trays are incubated at 35 °C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test
15 compound) used in each tray. The following test organisms were utilized in the assay:

gram positive bacteria

Enterococcus faecalis ATCC 29212

20 *Enterococcus faecalis* oc 3041

Enterococcus faecium oc 2993

Methicillin resistant *Staphylococcus aureus* oc 2089

Methicillin resistant *Staphylococcus aureus* oc667

Staphylococcus aureus ATCC 29213

25 *Staphylococcus aureus* ATCC 6538

Staphylococcus epidermidis oc 2603

Gram negative bacteria

Escherichia coli oc 2605

30 *Escherichia coli* oc 2530 ss

Klebsiella pneumoniae oc 1943

Pseudomonas aeruginosa oc 161

Pseudomonas aeruginosa ATCC 27853

P. aeruginosa oc 161

35 *P. aeruginosa* ATCC

The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are

illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

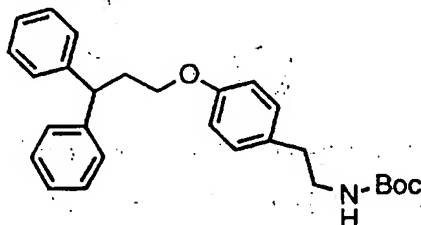
Methods of preparing the exemplified compounds of the invention are presented below. These examples are intended to illustrate the methods of synthesis, and are not intended to limit the scope of the claims in any way.

Abbreviations used: DEAD, diethyl azodicarboxylate; Ph_3P ,

triphenylphosphine; Bu_3P , tri-n-butylphosphine; THF, tetrahydrofuran; DMF, N,N-dimethylformamide; ADDP, 1,1'-(azodicarbonyl)dipiperidine; IPA, isopropanol; NMP, N-methylpyrrolidinone.

EXAMPLE 1

Preparation of Compound 1



N-t-BUTOXYCARBONYL-2-[4-(3,3-DIPHENYLPROPOXY)PHENYL]-ETHYLAMINE

Step 1a

N-(t-butoxycarbonyl)-2-(4-hydroxyphenyl)ethylamine

1a

Tyramine (5.58 g, 40.7 mmol) is dissolved in 50 mL of THF at 5 °C. Di-t-butyl dicarbonate (8.90 g, 40.8 mmol) in 25 mL of THF is added dropwise. The reaction is allowed to warm to ambient temperature overnight. After about 20 hours the reaction is diluted with water, extracted three times with EtOAc, dried over MgSO_4 and concentrated in vacuo. The crude brown solid, 8.93 g (93%) is used without further purification.

Step 1b

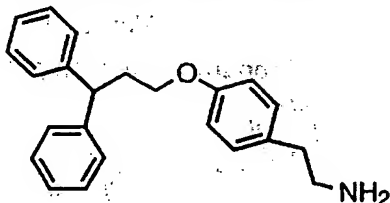
N-1-BUTOXYCARBONYL-2-[4-(3,3-DIPHENYLPROPOXY)-
PHENYLETHYLAMINE

Compound 1

- 5 Diethyl azodicarboxylate (1.3 mL, 8.1 mmol) in 10 mL of THF is added dropwise to a solution of THF (20 mL) containing 3,3-diphenylpropanol (1.8 g, 7.4 mmol), triphenylphosphine (2.1 g, 8.1 mmol) and 1a (1.9 g, 8.1 mmol) at room temperature. The progress of the reaction is monitored by TLC. The product is purified by flash chromatography (10% EtOAc/hexane) and
- 10 recrystallization from EtOAc/hexane to give 1.8 g (53%) of Compound 1.

EXAMPLE 2

Preparation of Compound 2

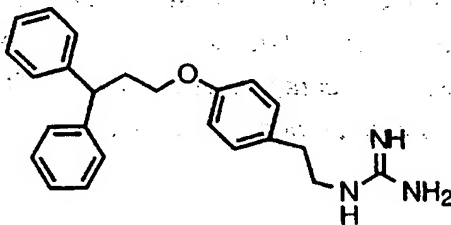


15 2-[4-(3,3-DIPHENYLPROPOXY)PHENYL]ETHYLAMINE

- A suspension of Compound 1, (1.01 g, 2.18 mmol), isopropanol (10 mL), and a 0.2g/mL solution of HCl (g) in IPA (5 mL) is heated until homogeneous, ca. 20 minutes. The completion of the reaction is determined by TLC. A white precipitate slowly forms upon cooling. This precipitate is
- 20 collected by filtration, washed with cold isopropanol and finally hexane, to give 650 mg (81%) of Compound 2 as the hydrochloride salt (mp =174-176°C).

EXAMPLE 3

Preparation of Compound 3



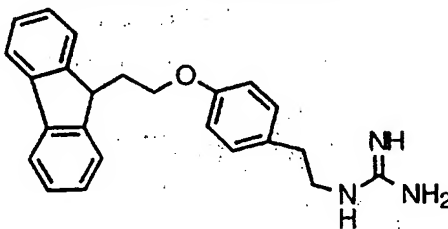
25 2-[4-(3,3-DIPHENYLPROPOXY)PHENYL]ETHYLGUANIDINE

Compound 2 (310 mg, 0.77 mmol) is combined with 3,5-dimethylpyrazole-1-carboxamide nitrate (170 mg, 0.84 mmol) and triethylamine (235 μ L, 1.6

- mmol) in DMF (5 mL). The reaction mixture is heated to 90 °C overnight. The preponderance of solvent is removed in vacuo. The remaining residue is dissolved in water and washed twice with ether. The aqueous layer is then stirred for 18 hours and a brown solid collected by filtration.
- 5 Recrystallization from water afforded Compound 3, 180 mg (63%) as a fine white powder (mp = 162-165°C).

EXAMPLE 4

Preparation of Compound 4



10 (2-[4-[2-(9-FLUORENYL)ETHOXY]PHENYL]ETHYL)GUANIDINE

Step 4a

N,N'-Bis(t-butoxycarbonyl)-N''-2-(4-hydroxyphenyl)ethylguanidine

4a

- 15 N,N'-Bis(t-butoxycarbonyl)-S-methoxyisothiourea (22.4 g, 77.3 mmol) prepared by the procedure set forth in Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* 1987, 52, 1700-1703 is dissolved in THF (130 mL) and added dropwise under nitrogen to tyramine (10.6 g, 77.3 mmol) in THF (100 mL) at 0°C (the liberated methyl sulfide is trapped with bleach). Reaction progress
- 20 is monitored by TLC. Upon completion, the solvent is removed in vacuo and purification is effected on a silica gel column. Successive elutions with 5% EtOAc/Hexane, 15% EtOAc/Hexane, and 35% EtOAc/Hexane, provided a white solid, in 72% yield (21.0 g).

Step 4b

25 (2-[4-[2-(9-FLUORENYL)ETHOXY]PHENYL]ETHYL)GUANIDINE

Compound 4

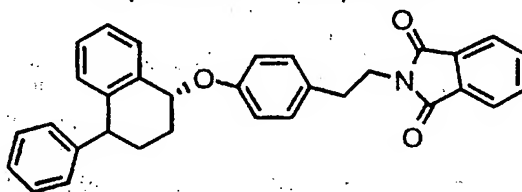
- 2-(9-Fluorenyl)ethanol (0.63 g, 3.0 mmol), intermediate 4a (1.14 g, 3.0 mmol) and triphenylphosphine (0.79 g, 3.0 mmol) in THF (5 mL) are
- 30 combined and cooled to 0 °C. Diethyl azodicarboxylate (0.48 mL, 3.0 mmol) in THF (5 mL) is added dropwise to this mixture. Spiro-9-fluorenylcyclopropane is a significant byproduct formed via competing intramolecular cyclization of the 2-(9-fluorenyl)ethanol. THF is removed in

vacuo and the residual solid is purified by flash chromatography (5% EtOAc/Hexane, then 10% EtOAc/Hexane) to give 0.60 g (35%) of a white solid. This white solid is subsequently dissolved in isopropanol (5 mL) and deprotected with a 0.2g/mL solution of HCl (g) in IPA (ca. 5 mL). The
5 deprotection proceeds to completion in about 4 hours at reflux. The final product, is collected as the bicarbonate salt from a biphasic mixture of EtOAc/ 0.5 N sodium bicarbonate. The white precipitate is washed with cold acetone followed by water, 145 mg (13%) (m.p. = 99 °C (dec.).

10

EXAMPLE 5

Preparation of Compound 5



2-[4-(4-PHENYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOXY)PHENYL]-
ETHYLPHthalimide

15

Step 5a

4-Phenyl-1,2,3,4-Tetrahydronaphthol

5a

Intermediate 5a was prepared according to the method of Kopecky, K. R.;

20 Hall M. C. *Can. J. Chem.* **1981**, 59, 3095-3104. See Sicsic, S., et. al. *J. Chem. Soc. Perkin Trans. 1*, **1992**, 3141-3144 for characterization of cis and trans-isomers.

Step 5b

25

2-(4-Hydroxyphenyl)ethylphthalimide

5b

2-(4-Hydroxyphenyl)ethylamine (6.14g, 44.8 mmol) and phthalic anhydride (6.63g, 44.8 mmol) are combined in ethanol (100 mL). Trifluoroacetic acid (3 mL) is added and the reaction is refluxed for 72 h. The precipitated solid
30 is collected and triturated with ethanol and hexane to give a tan solid 5.1 g (43%).

Step 5c

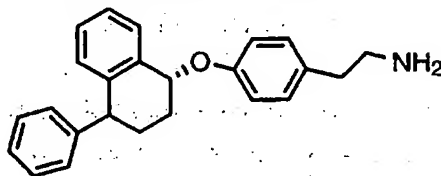
2-[4-(4-PHENYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOXY)PHENYL]-
ETHYLPHthalimide

Compound 5

- 5 **5b** (369 mg, 1.40 mmol) is combined with THF (5 mL), triphenylphosphine (398 mg, 1.50 mmol) and diethyl diazodicarboxylate (240 mL, 1.50 mmol) under nitrogen at room temperature. Note: **5b** dissolves upon addition of DEAD. The reaction is stirred for 10 minutes and **5a** (310 mg, 1.40 mmol) is added. After 24 hrs, the solvent is removed in vacuo and the product is
- 10 isolated by flash chromatography (5% EtOAc/ Hexane) as a clear oil, 210 mg (32 %).

EXAMPLE 6

Preparation of Compound 6

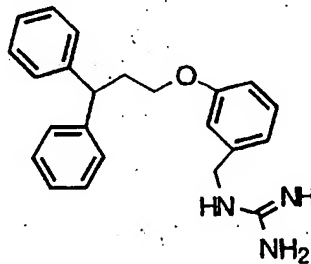
2-[4-(CIS-4-PHENYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOXY)PHENYL]-
ETHYLAMINE OXALATE

- Compound 5 (210 mg, 0.44 mmol) is heated to reflux for 2.5 hrs in 10% hydrazine/ ethanol. The resultant phthalhydrazide is filtered off and the
- 20 mother liquors are concentrated in vacuo. The residue is extracted with ether and any insoluble solids filtered away. The ether extracts are concentrated in vacuo to give a clear oil, 140 mg. The clear oil is dissolved in methanol, an oxalic acid-ether solution is added and the precipitate is collected, as a white solid, 80 mg (47%) (mp =205-207°C).

25

EXAMPLE 7

Preparation of Compound 7



[3-(3,3-DIPHENYLPROPOXY)PHENYL]METHYLGUANIDINE
BICARBONATE 0.5 HYDRATE

Step 7a

N,N'-Bis(t-butoxycarbonyl)-N''-2-(4-hydroxyphenyl)methylguanidine

5

7a

3-Hydroxyphenylmethylamine (42.6 mmol) and N,N'-bis-t-butoxycarbonyl-s-methoxyisothiurea (42.6 mmol) are combined with THF (50 mL) and stirred at room temperature for 48 hours (Inert Atmosphere, bubbled into bleach).

Work-up consisted of evaporation of solvent in vacuo and purification by
10 recrystallization from Hexanes/EtOAc to obtain 10.2 g of a white solid (65% yield).

Step 7b

[3-(3,3-DIPHENYLPROPOXY)PHENYL]METHYLGUANIDINE•
15 BICARBONATE•0.5-HYDRATE

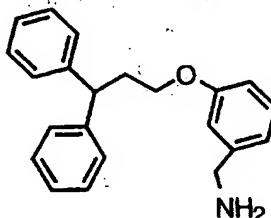
Compound 7

7a (2.36 mmol) and 3,3-diphenyl-1-propanol (2.36 mmol) are combined with tri-n-butylphosphine (2.47 mmol) and benzene (20 mL) under inert
20 atmosphere. Reaction is cooled to 0 °C and azodicarbonyldipiperidine (2.47 mmol) is added slowly. Reaction warmed to ambient temperature and stirred for 24 h. Reaction shown to be complete by TLC. Work-up consisted of evaporation of solvent in vacuo and purification by flash chromatography. Once purified, the protecting group is removed by dissolving the yellowish
25 oil in 0.2 g/mL solution of HCl in isopropanol (10 mL) and stirring overnight at room temperature under nitrogen. Stirring of the resulting oil with aqueous NaHCO₃/EtOAc afforded 0.047g (5.6%) of white solid, (mp=143-145 °C).

EXAMPLE 8

30

Preparation of Compound 8



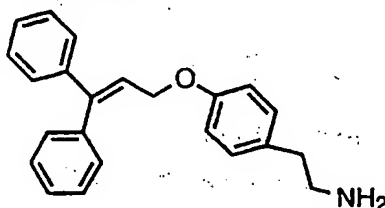
[3-(3,3-DIPHENYLPROPOXY)PHENYL]METHYLAMINE•
HYDROCHLORIDE•0.6 HYDRATE

7a (2.36 mmol) and 3,3-diphenyl-1-propanol (2.36 mmol) are combined with tri-*n*-butylphosphine (2.47 mmol) and benzene (20 mL). After 10 minutes, azodicarbonyldipiperidine (2.47 mmol) is added and reaction proceeded at room temperature under nitrogen. Reaction shown to be complete by TLC.

5 Workup consisted of evaporation of benzene *in vacuo* and purification by flash chromatography. The protecting group is removed by dissolving the oil in CH₂Cl₂ and adding 2-4 eq. TFA. This product is recrystallized from 3.0 N HCl/EtOH to afford an off-white crystals, 0.036g (4.8% yield) (mp=103-106 °C).

EXAMPLE 9

Preparation of Compound 9



2-[4-(3,3-DIPHENYL-2-PROPENOXY)PHENYL]ETHYLAMINE
HYDROCHLORIDE·0.5 HYDRATE

Step 9a

N-[2-(4-Hydroxyphenyl)ethyl]trifluoroacetamide

9a

4-Hydroxyphenylethylamine (21.4 mmol) and pyridine (24.6 mmol) is combined under nitrogen at 0 °C. Trifluoroacetic anhydride (24.6 mmol) are added slowly and reaction proceeds at 0 °C for one hour and then room temperature for 18 hours. The solvent is evaporated *in vacuo* and the residue is dissolved in CH₂Cl₂ and washed with successive portions of 1.0 N HCl and H₂O. The organic layer is dried and evaporated *in vacuo* to obtain N-[2-(4-hydroxyphenyl)ethyl]trifluoroacetamide as a white solid (86% yield).

Step 9b

2-[4-(3,3-DIPHENYL-2-PROPENOXY)PHENYL]ETHYLAMINE·
HYDROCHLORIDE·0.5 HYDRATE

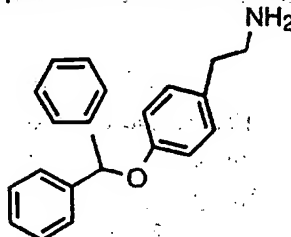
Compound 9

9a (2.37 mmol) and tri-*n*-butylphosphine (2.37 mmol) are combined with benzene (20 mL) at RT under nitrogen. After 10 minutes 3,3-diphenyl-2-propenol (2.37 mmol) is added. Finally, azodicarbonyldipiperidine (2.57 mmol) is added and reaction is stirred at RT for 18 hours. The reaction

- mixture is concentrated in vacuo and purified by flash chromatography. The protecting group is removed by dissolving the resulting oil in (10 mL) of aq. MeOH and acidifying with 1N HCl to pH=2-3. The solvent is removed in vacuo and the resulting brown solid is recrystallized from EtOH/Et₂O to
- 5 obtain 0.66g (70% yield) of light yellow powder (mp=91-96 °C).

EXAMPLE 10

Preparation of Compound 10



10

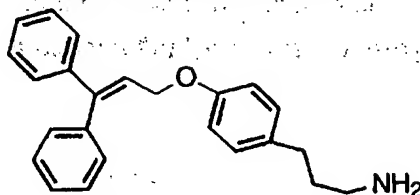
2-[4-(2-DIPHENYL-2-METHOXY)PHENYL]ETHYLAMINE•
HYDROCHLORIDE•HYDRATE

- 9a (1.65 mmol) and tri-*n*-butylphosphine (1.77 mmol) are combined with benzene (30 mL) at room temperature under nitrogen. After 10 minutes, benzhydrol (1.65 mmol) is added. Finally, azodicarbonyldipiperidine (1.77
- 15 mmol) is added and reaction is stirred for 18 hours. The solvent is removed in vacuo and purified by flash chromatography to obtain a white solid. The protecting group is removed using a MeOH/2N NaOH solution. Recrystallization from H₂O/1N HCl afforded 0.095g (19% yield) of white solid. (mp=140-145 °C).

20

EXAMPLE 11

Preparation of Compound 11



3-[4-(3,3-DIPHENYL-2-PROPENOXY)PHENYL]PROPYLAMINE•OXALATE

25

Step 11a

N-[3-(4-Hydroxyphenyl)propyl]trifluoroacetamide

11a

Intermediate 11a is prepared following the procedure of Step 9a. 2-(4-Hydroxyphenyl)ethylamine is replaced with 3-(4-hydroxyphenyl)propylamine to obtain the product, 0.55g (69.5%), as brown flakes.

Step 11b

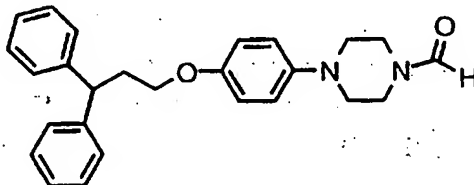
5 3-[4-(3,3-DIPHENYL-2-PROPENOXY)PHENYL]PROPYLAMINE•OXALATE

Compound 11

Intermediate 11a is combined with tri-n-butylphosphine (2.5 mmol) and benzene (20 mL). After 10 minutes, 3,3-diphenyl-2-propenol (2.2 mmol) is added. Finally, azodicarbonyldipiperidine (2.5 mmol) is added and reaction is stirred at room temperature for 24 h. Workup consists of evaporating solvent in vacuo and purifying by flash chromatography. The resulting residue is deprotected using a MeOH/2N NaOH solution. Once deprotected (TLC), solution is acidified to pH=3.0 using 1N HCl. Recrystallization from EtOAc/oxalic acid afforded the product, 0.038 g (4.8%) as a yellow solid, (mp=160-165 °C).

EXAMPLE 12

Preparation of Compound 12



20 1-FORMYL-4-[4-(3,3-DIPHENYLPROPOXY)PHENYL] PIPERAZINE• 0.5 HYDRATE

Step 12a

1 - Methanesulfonyloxy -3, 3-diphenylpropane

25 12a

Methanesulfonyl chloride (2.01 mL, 25.9 mmol) in CH₂Cl₂ (10 mL) is added over 10 min to a stirred solution of 3, 3-diphenylpropanol (5.0 g, 23.6 mmol) and Et₃N (4.92 mL, 35.3 mmol) in CH₂Cl₂ (260 mL), at -20 °C. Stirring is continued at that temperature for additional 1 h and the reaction mixture is allowed to warm to room temperature. The solution is washed with successive portions of H₂O, sat'd. NaHCO₃, 10% HCl, and H₂O, dried (Na₂SO₄), filtered, and concentrated in vacuo to obtain a solid: 6.83 g (100%), mp 88-90 °C; ¹H NMR (CDCl₃) δ 7.33-7.17 (m, 10H), 4.18-4.10 (m, 3H), 2.90 (s, 3H), 2.49 (q, J = 6.51, 2H). IR 1492, 1467, 1455, 1352, 1332, 1174,

959 cm^{-1} ; Anal. calc'd for $\text{C}_{16}\text{H}_{18}\text{O}_3\text{S}$: C, 66.18, H, 6.25; Found: C, 65.83, H, 6.16.

Step 12b

5 1-FORMYL-4-[4-(3,3-DIPHENYLPROPOXY)PHENYL] PIPERAZINE •
0.5 HYDRATE

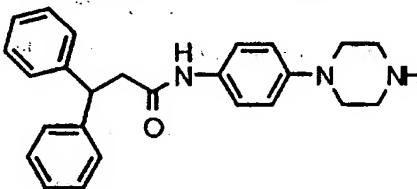
Compound 12

4-(4-Hydroxyphenyl)piperazine (0.356 g, 2 mmol) is added to a stirred
suspension of pentane washed 60% NaH (0.088 g, 2.2 mmol) in DMF (5
10 mL) under N_2 and the reaction mixture was heated to 60 °C for
approximately 10 min (until the effervescence ceased). Intermediate 12a
(0.319 g, 1.1 mmol) is added in one portion to the clear, dark solution and
the mixture is heated to 95 ° over 64 h. DMF is removed in vacuo and the
residue is taken up in CH_2Cl_2 , filtered and evaporated to dryness to obtain
15 an oily residue. This residue is purified by chromatography on silica using
increasing proportion of MeOH in CH_2Cl_2 containing 0.5 % Et_3N as the
eluent to give an oily residue, which crystallizes upon drying to a waxy solid,
mp 88- 90 °C; ^1H NMR (CDCl_3) δ 8.09 (s, 1H), 7.30-7.16 (m, 10H), 6.86 (d, J
= 9.10, 2H), 6.78 (d, J = 9.10, 2H), 4.23 (t, J=7.85, 1H), 3.85 (t, J = 6.40, 2H),
20 3.70 (t, J = 5.10, 2H), 3.52 (m, 2H), 3.02 (m, 4H), 2.50 (q, J = 6.41, 6.58, 2H);
IR: 1676, 1599, 1511, 1439, 1245, 1232 cm^{-1} ; MS 401 (MH^+). Anal. calc'd.
for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_2 \cdot 0.5 \text{H}_2\text{O}$: C, 76.25 ; H, 7.14 ; N, 6.84. Found : C, 76.27 ; H,
7.00 ; N, 6.96 .

25

EXAMPLE 13

Preparation of Compound 13



4-[4-(3,3-DIPHENYLPROPANOYLAMINO) PHENYL]PIPERAZINE •
0.5 HYDRATE

30

Step 13a

4-(4-Trifluoromethylacetamidophenyl)-1-trifluoroacetyl piperazine

13a

Triethylamine (7.42 mL, 26.63 mmol) is added to a solution of 4-(4-
aminophenyl)piperazine (4.29 g, 24.20 mmol) in CH_2Cl_2 (100 mL) at 0 °C.

A solution of trifluoroacetic anhydride (7.52 mL, 53.2 mmol) in CH_2Cl_2 (25 mL) is added over 5 min and the resulting mixture was stirred at 0 °C for 30 min, and allowed to warm up to room temperature over 72 h. Ice / H_2O is added and the resulting precipitate is removed and washed with CH_2Cl_2 , H_2O and sat NaHCO_3 . The solid is air dried to give **13a** as a solid: mp 193-194 °C.

Step 13b

4-[4-(3,3-DIPHENYLPROPANOYLAMINO)PHENYL]PIPERAZINE•

0.5 HYDRATE

Compound 13

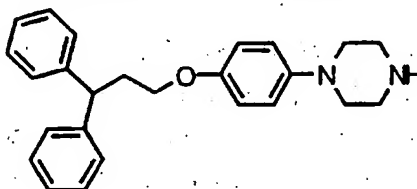
10

3, 3,-Diphenylpropionyl chloride (0.5384 g) is added to a mixture of **13a** (0.3693 g, 1 mmol) and anhydrous K_2CO_3 (1.105 g, 8.0 mmol) in CH_3CN (50 mL). This mixture is stirred and heated at 80 °C over the weekend. Following the TLC monitoring, four additional lots of the acid chloride (0.5384 g) and K_2CO_3 (1.105 g) are added every 3 h. while continuously refluxing under nitrogen. The resulting mixture is concentrated *in vacuo*, triturated with MeOH, filtered and the filtrate is evaporated to dryness *in vacuo*. The residue is stirred with 20% KOH/MeOH (15 mL) for 3 h. at room temperature and concentrated *in vacuo*. The residue is partitioned between H_2O and EtOAc and the organic layer extracted with 2 N HCl. The acid extract is basified with 2 N NaOH to pH 9.5 and extracted with EtOAc. The organic layer is washed (brine), dried (Na_2SO_4) and evaporated to dryness to give a light yellow solid residue (0.289 g, 75 %). Recrystallization from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ gives a solid: mp 178-179; ^1H NMR (CDCl_3) δ 7.32-7.18 (m, 10H), 7.13 (d, J = 8.91, 2H), 6.81 (d, J = 8.91, 2H) 4.63 (t, J = 7.70, 1H), 3.06-3.00 (m, 10H). IR 3309, 1650, 1602, 1515, 1495, 1451, 1235, 702 cm^{-1} . MS 386 (MH⁺). Anal. calc'd. for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O} \cdot 0.5 \text{H}_2\text{O}$: C, 76.11, H, 7.15, N, 10.65, Found : C, 76.26, H, 7.05, N, 10.56 .

30

EXAMPLE 14

Preparation of Compound 14

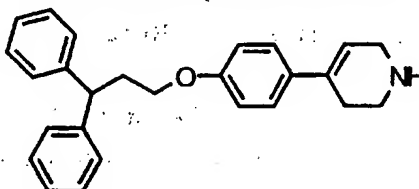


4-[4-(3,3-DIPHENYLPROPOXY)PHENYL]PIPERAZINE OXALATE

4-(4-Hydroxyphenyl)piperazine (0.356 g, 2 mmol) is added to a stirred a pentane washed suspension of 60% NaH (0.088 g, 2.2 mmol) in DMF (5 mL) under N₂ and the reaction mixture was heated to 60 °C for approximately 10 min (until the effervescence ceased). To the clear dark solution 3, 3-diphenyl-1-methanesulfonyloxypropane in NMP (3 mL) is added at once and the reaction mixture is heated to 90 °C over the weekend. (~65 h) NMP is removed in vacuo at 100 °C and the residue is taken up in CH₂Cl₂. The solution is washed (H₂O), separated, dried (Na₂SO₄) and evaporated in vacuo. The residue is purified by chromatography on silica using increasing proportion of MeOH in CH₂Cl₂ containing 0.5 % Et₃N. Two major products are isolated. The less polar one eluted with 4 % MeOH / CH₂Cl₂ (0.5 % Et₃N) as an oil (0.19 g) is characterized as the N, O-dialkylated product. MS 568 (MH⁺). The more polar product (desired), is eluted with 10 % MeOH/CH₂Cl₂ and obtained as an oil, 0.52 g (70 %), which crystallizes in to a waxy solid upon drying at 50 °C in vacuo: mp 114-116 °C. This compound is converted in to an oxalate salt by treatment with one equivalent of oxalic acid in i-PrOH and recrystallization from the same solvent: mp, decomposing above 170 °C. ¹NMR (CDCl₃) δ 7.60 (d, 2H), 7.40-7.24 (m, 8H), 7.19 (t, 2H), 7.06 (d, 2H), 5.71 (br s, H₂O / H⁺) 4.22 (t, 2H), 4.90 (t, 2H) 3.82 (b s, 2H), 3.59 (b s, 2H) 2.5 (bs, 2H, superimposed over DMSO signal). IR. 3440, 3080-2710, 2588, 1599, 1583, 1512, 1237, 702 cm⁻¹. MS 373 (MH⁺ free base). Anal. Calc'd. for C₂₅H₂₈N₂O•C₂H₂O₄: C, 70.11, H, 6.54, N, 6.06. Found: C, 70.65, H, 6.57, N, 6.19.

EXAMPLE 15

Preparation of Compound 15



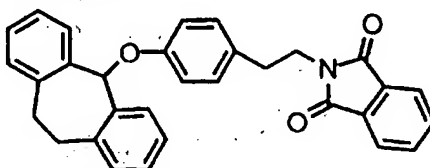
30 4-[4-(3,3-DIPHENYLPROPYLOXY)PHENYL]-1,2,3,6-TETRAHYDOPYRIDINE•HYDROCHLORIDE 0.6 HYDRATE

The title compound is prepared using the procedure of EXAMPLE 14 and substituting 4-(4-hydroxyphenyl)-1,2,3,6-tetrahydropyridine for the phenolic-amine. The free base of the title compound is obtained, after chromatography, as a solid (0.47 g, 64 %) which is converted to the

hydrochloride salt by passing dry HCl gas in i-PrOH. This salt is recrystallized from i-PrOH / EtO give an ivory solid: 0.322 g, mp, 155-6 °C; ¹H NMR (DMSO-d₆) δ 9.12 (s, 2H), 7.38-7.33 (m, 10H), 7.17 (m, 2H), 6.87 (d, J = 3.0, 2H), 6.06 (s, 1H), 4.21 (t, 1H), 3.86 (m, 2H), 3.70 (br s, 2H), 3.30 (m, 2H), 2.63 (br s, 2H); IR 3447-3419, 1514, 1243, 702 cm⁻¹. MS 370 (MH⁺, free base); Anal. calc'd. for C₂₆H₂₇NO•HCl•0.6 H₂O : C, 74.93, H, 7.06, N, 3.36. Found : C, 74.87, H, 7.04, N, 3.28.

EXAMPLE 16

Preparation of Compound 16

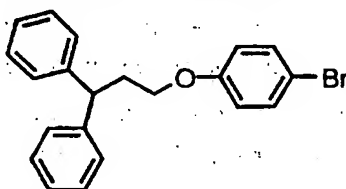


N-[2-[4-(10,11-DIHYDRO-5H-DIBENZO[a,d]CYCLOHEPTEN-5-OXY)-PHENYL]ETHYL]PHTHALIMIDE

Tri-*n*-butylphosphine (550 µL, 2.2 mmol) is added to a solution of dibenzosuberol (464 mg, 2.21 mmol) and intermediate **5b** (590 mg, 2.21 mmol) in benzene (10 mL) at 5 °C. 1,1'-(Azodicarbonyl)dipiperidine (557 mg, 2.21 mmol) is added and the resulting mixture is allowed to reach ambient temperature and remain there for 24 h. The resulting mixture is heated at reflux for an additional 24 h and concentrated *in vacuo*. The residue is purified by column chromatography using EtOAc/hexane (20:80) as an eluent to give 0.315 g (31%) of the title compound as a white solid mp: 205-207 °C; Anal. Calc'd for C₃₁H₂₅NO₃: C, 81.02; H, 5.48; N, 3.05; Found: C, 80.56; H, 5.4; N, 2.96

EXAMPLE 17

Preparation of Compound 17



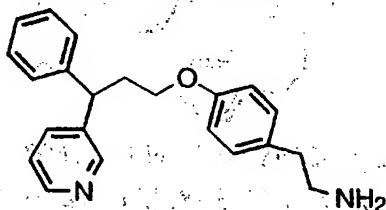
4-(3,3-DIPHENYLPROPOXY)BROMOBENZENE

A mixture of 4-bromophenol (1.73 g, 10 mmol), 1-methanesulphonyloxy -3,3-diphenylpropane (3.05 g, 10 mmol) and anhydrous potassium carbonate (2.07 g, 15 mmol) in acetonitrile (25 mL) is stirred and heated to reflux under nitrogen for 24 h. The reaction mixture is filtered, washed with acetone and the combined filtrate and washings are evaporated to dryness *in vacuo*. The

residue is taken up in Et₂O washed with successive portions of 5% aqueous NaOH and H₂O; dried (Na₂SO₄), filtered and concentrated in vacuo to give an oily residue (3.8 g) which crystallizes upon standing: mp 70-71 °C; ¹H NMR (CDCl₃) δ 7.35-7.16 (m, 12 H); 6.70 (d, 2 H, J = 8.98); 4.22 (t, 1 H, J = 7.9), 3.85 (t, 2 H, J = 6.), 2.54 (q, 2 H). IR 1592, 1490, 1470, 1291 cm⁻¹; MS 366 -368 (MH⁺, one Br); Anal. calc'd. for C₂₁H₁₉BrO : C, 68.86, H, 4.95. Found : C, 68.60, 5.18 .

EXAMPLE 18

Preparation of Compound 18



2-[4-(3-PHENYL-3-(3-PYRIDYL)PROPOXY)PHENYL]ETHYLAMINE·
OXALATE·0.1 HYDRATE

Step 18a

3-Phenyl-3-(3-pyridyl)-2-propen-1-ol

18a

Prepared in the manner of Hogberg, T, et al., *J. Org. Chem.* 1984, 49, 4209-4214 and references therein.

Step 18b

3-Phenyl-3-(3-pyridyl)propanol

18b

10% Pd/C (20 mg) is added to a mixture of isomeric 18a (360 mg, 1.70 mmol) in EtOH (10 mL) and the resulting mixture is treated with H₂ at 50 PSI for 20 h. The resulting mixture is filtered through celite and the filtrate is concentrated in vacuo to give 360 mg of the title compound as a yellow oil.

Step 18c

2-[4-(3-PHENYL-3-(3-PYRIDYL)PROPOXY)PHENYL]ETHYLAMINE·
OXALATE·0.1 HYDRATE

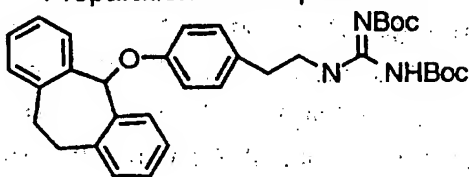
Compound 18

Triphenylphosphine (664 mg, 2.53 mmol) and diethylazodicarboxylate (400 μL, 2.5 mmol) are added to a solution of 18b (360 mg, 1.69 mmol) and 1c

(440 mg, 1.85 mmol) in THF (10 mL) at 22 °C. After 24 h the mixture is concentrated in vacuo and purified by column chromatography (45% EtOAc/hexane) to give a translucent solid. The product is recrystallized from MeOH/Et₂O to give 65 mg (10%) of the title compound as a solid: mp 202-203 °C Anal. Calc'd for C₂₂H₂₄N₂O•C₂H₂O₄•0.1 H₂O: C, 67.93; H, 6.77; N, 6.60; H₂O, 0.4; Found: C, 67.70; H, 6.38; N, 6.98; H₂O, 1.7.

EXAMPLE 19

Preparation of Compound 19

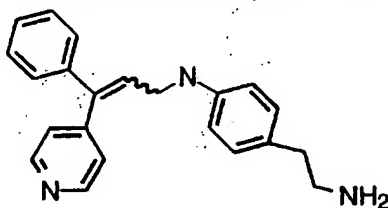


N,N'-BIS(t-BUTOXYCARBONYL)-N''-[2-[4-(10,11-DIHYDRO-5H-DIBENZO[a,d]CYCLOHEPTEN-5-OXY)-PHENYL]ETHYL]GUANIDINE

The title compound is prepared using the method of example 4 with the following modifications. Dibenzosuberol is used in place of 2-(9-fluorenyl)ethanol in step 4b and the protected product is isolated as a white solid.: mp 115-118; Anal. Calc'd for C₃₄H₄₁N₃O₅: C, 71.43; H, 7.23; N, 7.35; Found: C, 71.73; H, 7.24; N, 6.97

EXAMPLE 20

Preparation of Compound 20



Z-2-[4-(3-PHENYL-3-(3-PYRIDYL)PROPENYLAMINO)PHENYL]-ETHYLAMINE•OXALATE•0.2 DIETHYL ETHER•

0.15 ETHYL ACETATE•0.5 HYDRATE

Step 20a

3-Phenyl-3-(3-pyridyl)-2-propen-1-al

20a

Prepared in the manner of Hogberg, et al. *Journal Of Organic Chemistry* 1984, 22, 4209-4214.

Step 20b

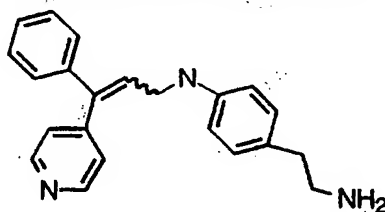
**Z-2-[4-(3-PHENYL-3-(3-PYRIDYL)-2-PROPENYLAMINO)PHENYL]-
ETHYLAMINE•OXALATE•0.2 DIETHYL ETHER•
0.15 ETHYL ACETATE•0.5 HYDRATE**

5 Ratio E/Z 4:1

- Sodium cyanoborohydride (220 mg, 3.5 mmol) is added portionwise to **20a** (730 mg, 3.49 mmol) and N-[2-(4-aminophenyl)ethyl]trifluoroacetamide (810 mg, 3.49 mmol) in 15% AcOH/MeOH (35 mL) at 5 °C. After 1 h the mixture is concentrated in vacuo and partitioned between H₂O and CHCl₃. The aqueous layer is washed with several portions of CHCl₃ and the combined extracts are dried (MgSO₄) and concentrated in vacuo. The residue is purified by column chromatography (40% EtOAc/hexane) to give the amino protected products, A (780 mg), a 4:1 **Z** enriched isomer and B (400 mg), a 4:1 **E** enriched isomer. Product A is deprotected using 2 equivalents of 2M NaOH in MeOH (5 mL) at room temperature. The product is isolated by removing the solvent, partitioning the residue between EtOAc and H₂O; drying the combined organic layers (MgSO₄) and concentrating in vacuo. The residue is treated with MeOH, EtOAc and oxalic acid to give 560 mg, of the title compound as a solid: mp 126-128 °C; Anal. Calc'd for
- 20 C₂₂H₂₃N₃•C₂H₂O₄•0.2 C₄H₁₀O•0.15 C₄H₈O₂•0.5 H₂O: C, 66.83 ;H, 6.54 N, 9.20 H₂O, 1.9 Found: C, 66.65 H, 6.24 N, 9.28; H₂O, 1.6.

EXAMPLE 21

Preparation of Compound 21



25

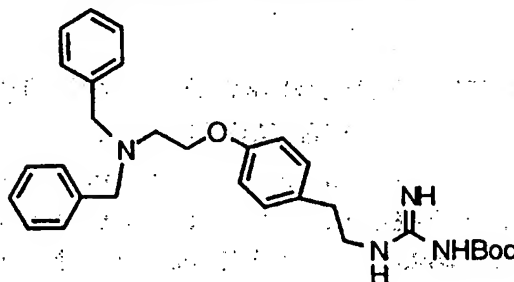
**E-2-[4-(3-PHENYL-3-(3-PYRIDYL)-2-PROPENYLAMINO)PHENYL]-
ETHYLAMINE•OXALATE•0.33 ETHYL ACETATE•0.5 HYDRATE**

- Product B (from Example 20) is deprotected using 2 equivalents of 2M NaOH in MeOH (5 mL) at room temperature. The product is isolated by removing the solvent, partitioning the residue between EtOAc and H₂O; drying the combined organic layers (MgSO₄) and concentrating in vacuo. The residue is treated with MeOH, EtOAc and oxalic acid to give 110 mg, of the title compound as a solid: mp 120-122 °C Anal. Calc'd for
- 30

$C_{22}H_{23}N_3 \cdot C_2H_2O_4 \cdot 0.33 C_4H_8O_2 \cdot 0.5 H_2O$: C, 66.46; H, 6.37 N, 9.18 H₂O,
1.9 Found: C, 66.04 H, 6.17 N, 9.10; H₂O, 1.8.

EXAMPLE 22

Preparation of Compound 22

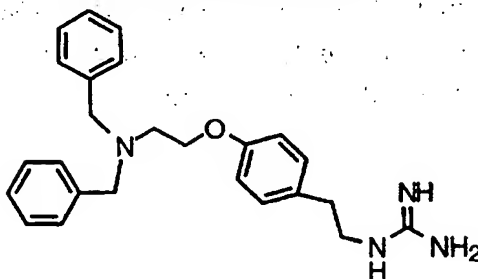


N,N'-BIS (1-BUTOXYCARBONYL)-N''-(2-[4-(2-[N,N'-DIBENZYLAMINO]-
ETHOXY)PHENYL]ETHYLGUANIDINE)

Triphenylphosphine (1.2 eq) is added to a solution of **4a** in benzene
(30 mL). 2-(Dibenzylamino)ethanol and 1,1-(azodicarbonyl)dipiperidine
(1.2 eq) are added sequentially and the mixture is stirred at room
temperature for 16 h. The resulting mixture is concentrated in *in vacuo* and
purified by column chromatography using CH₂Cl₂ to give a solid. This solid
is treated with HCl/IPA (20 mL) at room temperature for 2-4 h, concentrated
in vacuo and recrystallized from EtOAc to give 593 mg of the title compound
as a solid: mp 125-130 °C.

EXAMPLE 23

Preparation of Compound 23

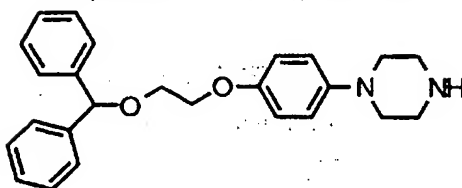


2-[4-(2-[N,N'-DIBENZYLAMINO]-ETHOXY)PHENYL]ETHYLGUANIDINE

Compound 23 was prepared in a similar manner to compound 22. The Boc-
protected guanidine was treated to three equivalents of TFA to give
Compound 24 as an oil. Anal. calc'd for C₂₅H₃₀N₄O \cdot 3.0 CF₃CO₂H: C,
50.00; H, 4.47; N, 7.52; Found: C, 50.30; H, 4.99; N, 7.26.

EXAMPLE 24

Preparation of Compound 24

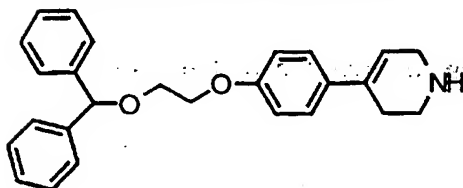


4-[4-(2-(DIPHENYLMETHOXY)ETHOXY)PHENYL]PIPERAZINE •
CARBONATE 2.0 HYDRATE

- 5 4-(4-Hydroxyphenyl)piperazine (0.356 g, 2 mmol) is added to a stirred suspension of NaH (0.088 g of 60 % oil dispersion (2.2 mmol)), washed and decanted with pentane) in DMF (5 mL) under N₂ and the reaction
- 10 mixture was heated to 70 °C for approximately 10 min (until the effervescence ceased). Benzhydrylchloroethylether (0.542 g, 2.2 mmol) in DMF (1.5 mL) was added, followed by NaI (0.331 g, 2.2 mmol). The reaction mixture was stirred and heated to 90-100 °C for 48 h. DMF was removed in vacuo and the residue triturated in CHCl₃. The insoluble solids removed by filtration, washed (CHCl₃) and the combined organic extracts were washed
- 15 with water, dried (Na₂SO₄) and evaporated in vacuo to afford an oily residue (1 g). The residue is purified by column chromatography on silica gel using an increasing proportion of MeOH in CH₂Cl₂ containing 0.5 % Et₃N to give a colorless foamy solid (0.416 g, 53 %). Traces of residual Et₃N are removed by washing with CH₂Cl₂, dried (Na₂SO₄) and evaporation in vacuo to afford
- 20 shiny crystalline flakes: mp 106-108 °C: ¹H NMR (DMSO-d₆) δ 9.14 (s, 1H), 7.4-7.2 (m, 10H), 6.91 (q, 4H), 5.57 (s, 1H), 4.12 (t, 2H), 3.71 (t, 2H), 3.21 (br s, 8H): IR 3361, 2925, 2834, 1674, 1516, 1496, 1452, 1252 cm⁻¹. MS 389 (MH⁺). Anal. Calc'd. for C₂₅H₂₈N₂O₂ • H₂CO₃ • 2 H₂O : C, 64.18, H, 7.04, N, 5.76. Found : C, 64.49, H, 6.85, N, 6.06.
- 25

EXAMPLE 25

Preparation of Compound 25



4-[4-[2-(DIPHENYLMETHOXY) ETHOXY] PHENYL]-1, 2, 3, 6-
TETRAHYDROPYRIDINE•MONOOXALATE 0.5 HYDRATE

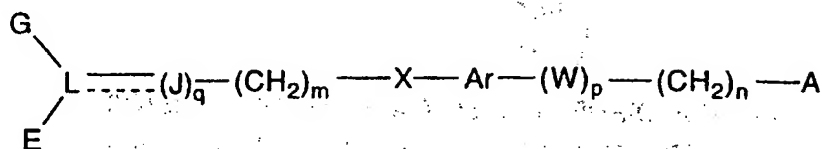
5 The title compound is prepared using the procedure of EXAMPLE 25 and substituting 4-(4-hydroxyphenyl)-1,2,3,6-tetrahydropyridine for the phenolic-amine. The title compound is obtained, after chromatography, as an oil (0.28 g, 36 %) which is converted to the oxalate salt by treatment with one
10 equivalent of oxalic acid in i-PrOH. Recrystallization from i-PrOH/Et₂O gives a crystalline solid 0.209 g: mp 154-156 °C; ¹H NMR (DMSO-d₆) δ 9.10 (br s, 2H), 7.43-7.20 (m, 12H), 6.97 (d, J = 8.8, 2H), 6.09 (s, 1H), 5.56 (s, 1H), 4.19 (m, 2H), 3.73 (m, 4H), 2.69 (br s, 2H); IR 3448-3407, 1652, 1645, 1607, 1514, 1232, 1187 cm⁻¹; MS 389 (MH⁺, free base); Anal. calc'd: for
15 C₂₆H₂₇NO₂•C₂H₂O₄•0.5 H₂O : C, 69.41, H, 6.24, N, 2.89. Found : C, 69.16, H, 6.02, N, 3.09.

CLAIMS

We claim:

1. A compound selected from those of the Formula I:

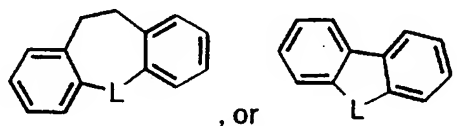
5



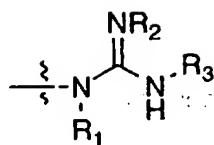
wherein

L is selected from the group consisting of N, CH and C;

10 G and E are independently selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), phenylC₁₋₄alkyl, substituted phenylC₁₋₄alkyl (where the phenyl substituents are hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl and 3-thienyl,
15 or may be taken together with L (when L is CH), to form



20 J is CH or O;
q is 0 or 1;
m is 0-6;
X is selected from the group consisting of O, S, NR and -C(O)NR- where R is hydrogen, C₁₋₆alkyl and phenylC₁₋₄alkyl;
25 Ar is aryl or substituted aryl (where the aryl substituents are hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), wherein aryl is phenyl, biphenyl or naphthyl;
p is 0 or 1
W is O or S
30 n is 0-6
A is selected from the the group consisting of NR₁R₂, N+R₁R₂R₃ • Z-



, amidino, CO₂H, CH(R₄)CO₂H, CH=CHR₅,
 CH=C(CO₂H)₂, halogen, phthalimido and a heterocycle, optionally
 substituted with 1-3 substituents (where the substituents are
 selected from C₁₋₆alkyl, phenylC₁₋₄alkyl, formyl, C₁₋₃alkylcarbonyl
 and trifluoroalkylcarbonyl),

wherein:

R₁, R₂, and R₃ are independently selected from
 hydrogen, C₁₋₆alkyl, and phenylC₁₋₆ alkyl;

R₄ is hydrogen or hydroxy;

R₅ is CO₂H or C(O)NH(CH₂)_tOH where t is 1-4;

Z- is a pharmaceutically acceptable counterion;

heterocycle is a saturated or unsaturated, charged or
 uncharged 5 to 6 membered monocyclic ring which has 1, 2, or
 3 heteroatoms independently selected from oxygen, nitrogen
 and sulfur atoms;

with the proviso that:

when q is 1 and J is CH, L is C, m is at least 1 and the dashed line
 is taken together with the solid line to form a double bond;

when q is 1 and J is O, L is CH, m is at least 2 and the dashed line
 is absent;

when q is 0, L is N or CH and the dashed line is absent;

when q and m are 0, L is CH;

when n is 0, A may also be hydroxy;

when X is C(O)NH, A is not CO₂H; and

where n is 0 or 1, and W is O or S, A is not OH, NR₁R₂ or a
 heteroatom;

and the pharmaceutically acceptable salts and prodrug forms thereof.

2. The compound of claim 1 wherein

G and E is phenyl, substituted phenyl, phenylC₁₋₄alkyl or substituted
 phenylC₁₋₄alkyl ;

q is 0;

m is 2;

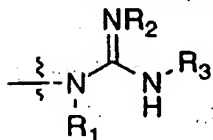
X is O or S;

Ar is 1,4-phenylene, 1,4- naphthylene or 1,6-naphthylene;

p is 0;

n is 0-3;

A is NR_1R_2 , $\text{N}^+\text{R}_1\text{R}_2\text{R}_3 \cdot \text{Z}^-$, halogen, phthalimido, amidino,



, or a heterocycle, optionally substituted with 1-3 substituents.

3. The compound of claim 1 wherein

G and E are phenyl, substituted phenyl, phenylC₁₋₄alkyl or substituted phenylC₁₋₄alkyl ;

q is 1;

J is CH;

m is 1;

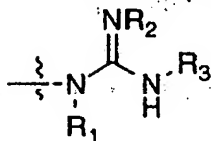
X is O, NR or S;

Ar is 1,4-phenylene, 1,4- naphthylene or 1,6-naphthylene;

p is 0;

n is 0-3;

A is NR_1R_2 , $\text{N}^+\text{R}_1\text{R}_2\text{R}_3 \cdot \text{Z}^-$, halogen, phthalimido, amidino,



, or a heterocycle, optionally substituted with 1-3 substituents.

4. The compound of claim 1 wherein

G and E are phenyl, substituted phenyl, phenylC₁₋₄alkyl or substituted phenylC₁₋₄alkyl ;

q is 0;

m is 0;

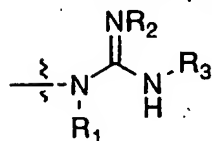
X is O or S;

Ar is 1,4-phenylene, 1,4- naphthylene or 1,6-naphthylene;

p is 0;

n is 0-3;

A is NR_1R_2 , $\text{N}^+\text{R}_1\text{R}_2\text{R}_3 \cdot \text{Z}^-$, halogen, phthalimido, amidino,



, or a heterocycle, optionally substituted with 1-3 substituents.

5. The compound of claim 1 wherein

G and E are phenyl, substituted phenyl, phenyl C_{1-4} alkyl or substituted phenyl C_{1-4} alkyl;

q is 1;

J is O;

10 m is 2;

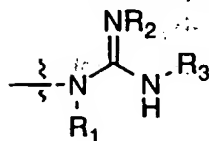
X is O or S;

Ar is 1,4-phenylene, 1,4-naphthylene or 1,6-naphthylene;

p is 0;

n is 0-3;

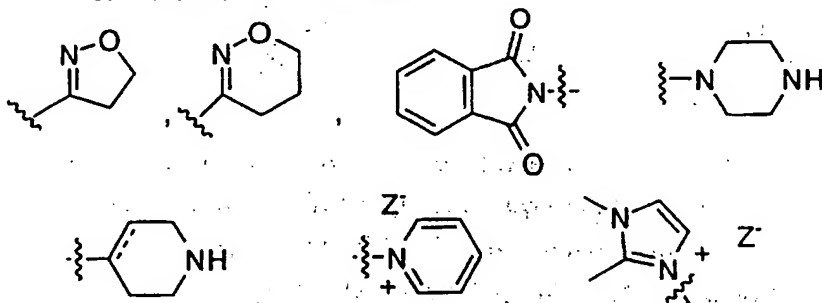
15 A is NR_1R_2 , $\text{N}^+\text{R}_1\text{R}_2\text{R}_3 \cdot \text{Z}^-$, halogen, phthalimido, amidino,



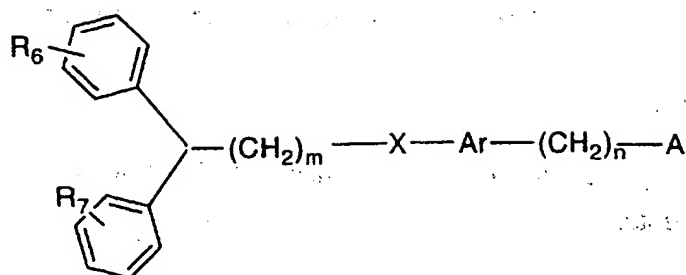
, or a heterocycle, optionally substituted with 1-3 substituents.

6. The compound of claim 1 wherein

20 A is NR_1R_2 , $\text{N}^+\text{R}_1\text{R}_2\text{R}_3 \cdot \text{Z}^-$, amidino, guanidino or moieties the formulae



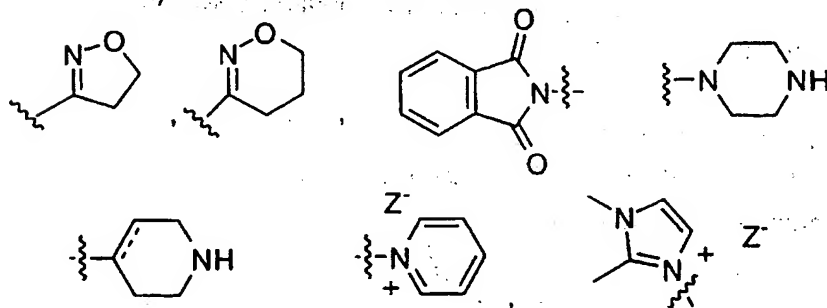
7. The compound according to claim 1 of the Formula III



III

wherein

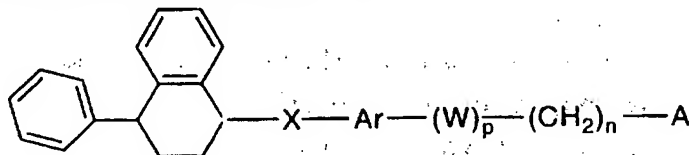
- 5 R_6 and R_7 are independently selected from H, halogen, C₁-6alkyl and C₁-6alkoxy;
 m is 1 or 2;
 X is selected from O, and S;
 Ar is selected from 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene;
 10 wherein Ar may optionally be further substituted with one to three substituents selected from halogen, C₁-6alkyl, hydroxy, or C₁-6alkoxy;
 n is 1, 2, or 3;
 and A is selected from NR_1R_2 , guanidino, $N^+R_1R_2R_3 Z^-$ (wherein R_1 , R_2 , and R_3 are independently H, C₁-6alkyl, or aryl-C₁-6alkyl and wherein Z^- is a pharmaceutically acceptable anion) and moieties of the formula:



8. The compound of claim 1 selected from the group consisting of N-*t*-butoxycarbonyl-2-[4-(3,3-diphenylpropoxy)phenyl]-ethylamine, 2-[4-(3,3-diphenylpropoxy)phenyl]ethylamine, 2-[4-(3,3-diphenylpropoxy)-phenyl]ethylguanidine and {2-[4-[2-(9-fluorenyl)ethoxy]-phenyl]ethyl}guanidine.
9. The compound of claim 1 selected from the group consisting of [3-(3,3-diphenyl-propoxy)-phenyl]methylguanidine, N,N'-bis (*t*-butoxycarbonyl)-N"-

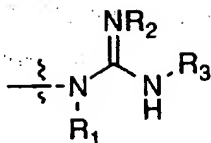
{2-[4-(2-[N,N'-dibenzylamino]ethoxy)phenyl]ethylguanidine}, 2-[4-(2-[N,N'-dibenzylamino]ethoxy)phenyl]ethylguanidine and [3-(3,3-diphenylpropoxy)-phenyl]-methylamine.

- 5 10. The compound of claim 1 selected from the group consisting of 2-[4-(3,3-diphenyl-2-propenoxy)phenyl]ethylamine, 2-[4-(1,1-diphenyl-2-methoxy)-phenyl]ethylamine, 3-[4-(3,3-diphenyl-2-propenoxy)phenyl]propylamine and 1-formyl-4-[4-(3,3-diphenylpropoxy)phenyl] piperazine.
- 10 11. The compound of claim 1 selected from the group consisting of 4-[4-(3,3-diphenylpropanoylamino) phenyl]piperazine, 4-[4-(3,3-diphenylpropoxy) phenyl]piperazine, 4-[4-(3,3-diphenyl-propyloxy)phenyl]-1,2,3,6-tetrahydropyridine and N-{2-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-oxy)-phenyl]ethyl}phthalimide.
- 15 12. The compound of claim 1 selected from the group consisting of 4-(3,3-diphenylpropoxy)bromobenzene, 2-[4-(3-phenyl-3-(3-pyridyl)propoxy)phenyl]ethylamine, N,N"-bis(t-butoxycarbonyl)-N"-{2-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-oxy)-phenyl]ethyl}guanidine and 2-[4-(3-phenyl-3-(3-pyridyl)-2-propenylamino)phenyl]-ethylamine.
- 20 13. A compound selected from those of the Formula II:



25 wherein:

- X is selected from the group consisting of O, S, NR and -C(O)NR- where R is hydrogen, C₁₋₆alkyl and phenylC₁₋₄alkyl;
- Ar is aryl or substituted aryl (where the aryl substituents are hydrogen, halogen, C₁₋₆alkyl or C₁₋₆alkoxy), wherein
- 30 aryl is phenyl, biphenyl or naphthyl;
- p is 0 or 1
- W is O or S
- n is 0-6
- A is selected from the the group consisting of NR₁R₂, N⁺R₁R₂R₃ • Z⁻.



, amidino, CO₂H, CH(R₄)CO₂H, CH=CHR₅,
 CH=C(CO₂H)₂, halogen, phthalimido and a heterocycle, optionally
 substituted with 1-3 substituents (where the substituents are
 selected from C₁₋₆alkyl, phenylC₁₋₄alkyl, formyl, C₁₋₃alkylcarbonyl
 and trifluoroalkylcarbonyl),

wherein:

R₁, R₂, and R₃ are independently selected from
 hydrogen, C₁₋₆alkyl, and phenylC₁₋₆ alkyl;

R₄ is hydrogen or hydroxy;

R₅ is CO₂H or C(O)NH(CH₂)_tOH where t is 1-4;

Z⁻ is a pharmaceutically acceptable counterion;

heterocycle is a saturated or unsaturated, charged or
 uncharged 5 to 6 membered monocyclic ring which has 1, 2, or
 3 heteroatoms independently selected from oxygen, nitrogen
 and sulfur atoms;

with the proviso that:

when q is 1 and J is CH, L is C, m is at least 1 and the dashed line
 is taken together with the solid line to form a double bond;

when q is 1 and J is O, L is CH, m is at least 2 and the dashed line
 is absent;

when q is 0, L is N or CH and the dashed line is absent;

when q and m are 0, L is CH;

when n is 0, A may also be hydroxy;

when X is C(O)NH, A is not CO₂H; and

where n is 0 or 1, and W is O or S, A is not OH, NR₁R₂ or a
 heteroatom;

and the pharmaceutically acceptable salts and prodrug forms thereof.

14. The compound of claim 13 wherein

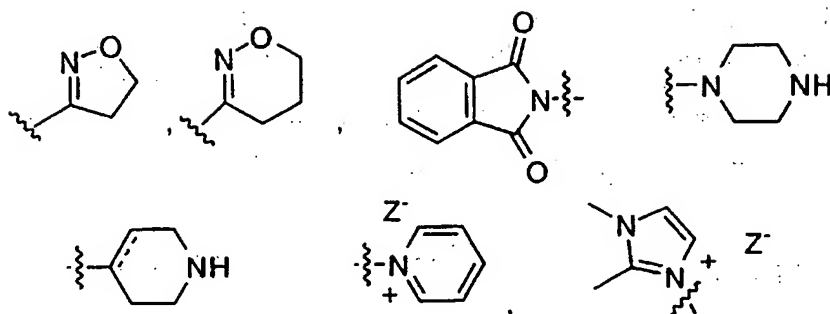
Ar is 1,4-phenylene, 1,4-naphthylene or 1,6 naphthylene;

X is O or S;

p is 0;

n is 0-3;

A is NR₁R₂, N⁺R₁R₂R₃ • Z⁻, halogen, amidino, guanidino, phthalimido
 or moieties the formulae



15. The compound of claim 12 selected from the group consisting of 2-[4-(cis-4-phenyl-1,2,3,4-tetrahydro-1-naphthoxy)phenyl]-ethylphthalimide and 2-[4-(cis-4-phenyl-1,2,3,4-tetrahydro-1-naphthoxy)phenyl]-ethylamine.

16. A method of treating bacterial infections in mammals by administering to a mammal suffering from such infection a therapeutically effective amount of a compound selected from those of claim 1 or claim 13.

17. A pharmaceutical composition for treating bacterial infections comprising an effective amount of a compound selected from claim 1 or claim 13, in association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Intern. nat Application No

PCT/US 97/09955

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C217/56 C07C271/16 C07C279/08 C07C43/225 C07D295/135
C07D295/096 C07D211/70 C07D213/30 C07D209/48 C07D213/53
A61K31/135 A61K31/325 A61K31/17 A61K31/40 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 839 451 A (J.D. HUNT ET AL.) 1 October 1974 see example II	1,6
X	I.A. KAYE ET AL.: "Thiocyanation of p-dialkylaminoalkoxyanilines" JOURNAL OF ORGANIC CHEMISTRY, vol. 16, no. 9, 1951, WASHINGTON DC, US, pages 1421-6, XP002042075 see page 1424, table II, No. II, C	1,6
X	M. MURAMATSU ET AL.: "The cycloaddition reaction of isonitriles (the reaction of isonitriles with diazoalkane)" TETRAHEDRON LETTERS, no. 23, 1973, OXFORD, GB, pages 2133-6, XP002042076 see page 2134, compound XI	1,6

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

29 September 1997

Date of mailing of the international search report

-7. 10. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 97/09955

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G.S. HAMILTON ET AL.: "Fluorenylalkanoic and benzoic acids as novel inhibitors of cell adhesion processes in leukocytes" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 10, 1995, WASHINGTON DC, US, pages 1650-6, XP002042077 see the whole document, particularly page 1653, table 2, and page 1654, table 3	1,17
X	F. EL-ZAHRAA ET AL.: "Synthesis and pharmacological screening of certain N-substituted amides structurally related to some local anesthetics" PHARMAZIE, vol. 34, no. 1, 1979, BERLIN, DE, pages 12-3, XP002042078 see the whole document, particularly page 12, scheme 1, compounds 8, 9, 11 and 12	1,17

-/-

☒ Further documents are listed in the continuation of box C.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 September 1997

Date of mailing of the international search report

7. 10. 97

Name and mailing address of the ISA

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Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 97/09955

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>T. SOHDA ET AL.: "Studies on antidiabetic agents. II. Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its derivatives"</p> <p>CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 30, no. 10, 1982, TOKYO, JP, pages 3580-600, XP002042079</p> <p>see the whole document, particularly page 3584, chart 10 and table II, compound 27</p>	1,7,17
X	<p>DATABASE CROSSFIRE</p> <p>Beilstein Informationssysteme GmbH, Frankfurt DE</p> <p>XP002042080</p> <p>see BRN=2386379 and 2386380</p> <p>& CHEMICAL ABSTRACTS, vol. 92, no. 5, 1980</p> <p>Columbus, Ohio, US;</p> <p>abstract no. 41510j,</p> <p>page 743;</p> <p>&</p> <p>YAKUGAKU ZASSHI,</p> <p>vol. 99, no. 7, 1979,</p> <p>pages 779-81,</p>	1,17
X	<p>DATABASE CROSSFIRE</p> <p>Beilstein Informationssysteme GmbH, Frankfurt DE</p> <p>XP002042081</p> <p>see BRN=2882098 and 2869192</p> <p>&</p> <p>REV. PORT. FARM.,</p> <p>1968,</p> <p>pages 113-22,</p>	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/09955

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97 09955

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1-7

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In view of the extremely large number of possible classes of compounds covered by formula I of claim 1 and the absence of any significant structural distinguishing feature in said formula on the one hand, and the large number of already known compounds covered by claims 1-7 on the other hand, the search and the search report for said claims 1-7 cannot be considered as complete, see PCT Search Guidelines (PCT/GL/2), Chapter III, 2.1 and 3.7.

Remark : Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 97/09955

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3839451 A	01-10-74	US 3625913 A	07-12-71
